Chronically increased sleep pressure: Electrophysiological correlates and behavioral consequences

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1 Summary

Sleep pressure increases during wakefulness and dissipates during sleep. Chronic sleep restriction (SR), i.e., obtaining chronically less sleep than needed, is highly prevalent in society. Nevertheless, most research in the past focused on the effects of acute sleep deprivation (SD), which refers to a one-time prolongation of wakefulness.

Data presented in this thesis were obtained in a controlled, laboratory, within-subject design study with healthy individuals undergoing SD and SR, and in a controlled, prospective clinical study in traumatic brain injury (TBI) patients.

While electrophysiological markers of increased sleep pressure and induced impairments in basic behavioral functioning were higher after SD than SR, these changes were associated across both conditions. Complex behavior, i.e., decision-making, was affected in a less linear manner: only SR but not SD resulted in increased risk-seeking. This increase was subjectively not noticed and linked to locally insufficient brain recovery during sleep. Further findings were a sleep loss induced change in sleep perception and the underestimation of increased sleep pressure in TBI patients.

Taken together, this thesis contributes to the understanding of the extent to which effects of increased sleep pressure following SD also apply to SR, to insights into possible underlying mechanisms of behavioral changes following SR and to the identification of aspects which may be relevant for clinical contexts.

2 Zusammenfassung

Schlafdruck wird während dem Wachsein auf- und während dem Schlaf abgebaut. In der Gesellschaft ist eine chronisch zu kurze Schlafdauer, genannt Schlafrestriktion (SR), weit verbreitet. Trotzdem wurden bisher vor allem die Folgen der Schlafdeprivation (SD) untersucht, was einem einmalig längeren Wachsein entspricht.

Die Daten, welche dieser Dissertation zugrunde liegen, stammen aus einer kontrollierten, experimentellen Studie mit gesunden Probanden, die eine SD und SR durchliefen und einer kontrollierten, prospektiven Studie bei Schädel-Hirn-Trauma (SHT) Patienten.

Während die elektrophysiologischen Masse für erhöhten Schlafdruck und die Beeinträchtigungen in elementaren Verhaltensweisen nach SD stärker ausgeprägt waren als nach SR, hing das Ausmass der Veränderungen zwischen beiden Bedingungen zusammen. Die Veränderung in komplexen Verhaltensweisen, hier in der Entscheidungsfindung, war weniger linear: Nur nach SR nicht aber nach SD stieg die Risikofreude. Der Anstieg wurde subjektiv nicht bemerkt und korrelierte mit lokal niedriger Erholung des Gehirns während des Schlafs. Weitere Befunde waren eine durch Schlafmangel induzierte Veränderung der Schlafwahrnehmung und eine Unterschätzung des erhöhten Schlafdrucks in SHT Patienten.

Insgesamt trägt diese Dissertation zum Verständnis bei, inwiefern Folgen der SD und SR vergleichbar sind und zeigt mögliche Mechanismen, die den Verhaltensänderungen durch SR zugrunde liegen sowie klinisch relevante Aspekte ungenügenden Schlafs auf.

3 Introduction

More than 30% of individuals in various countries report to obtain less than the recommended minimal amount of seven hours of sleep per night on a regular basis (Groeger, Zijlstra, & Dijk, 2004; Liu et al., 2016; Tinguely, Landolt, & Cajochen, 2014; Watson et al., 2015b). Furthermore, there is some – albeit not undisputed – evidence that the frequency of short sleep durations seems to increase in our 24/7 society (Banks & Dinges, 2007; Basner, Rao, Goel, & Dinges, 2013; Luckhaupt, Tak, & Calvert, 2010; Tinguely et al., 2014), either due to prolonged working hours, increasing commute times, personal lifestyle or other reasons (Basner et al., 2007). Sleepiness-related performance impairments and accidents resulting in high socio-economic costs are only some of the potential consequences of chronically inadequate sleep durations (Lockley et al., 2004; Rosekind et al., 2010; Watson et al., 2015b). The negative effects of insufficient sleep may even reach clinically relevant levels and result in the condition of the insufficient sleep syndrome (ISS; *American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). Despite the high prevalence and potential negative consequences of chronically short sleep durations in modern society (Groeger et al., 2004; Liu et al., 2016; Lockley et al., 2004; Rosekind et al., 2010; Tinguely et al., 2014; Watson et al., 2015b), most studies in the past focused on the effects of increased sleep pressure resulting from acute sleep deprivation (SD), which corresponds to a one-time prolongation of wakefulness, e.g., one night without sleep. In contrast, the effects of chronic sleep restriction (SR), which corresponds to a reduction in sleep duration for several consecutive nights, have been less extensively studied so far (e.g., Banks & Dinges, 2007). As a result, the effects and underlying mechanisms of chronic SR remain unknown for a variety of cognitive domains (Watson et al., 2015a) and it is also unclear which aspects of increased sleep pressure following acute SD also apply to the condition of chronic SR (Basner et al., 2013; Drummond, Anderson, Straus, Vogel, & Perez, 2012; Philip et al., 2012; Rowland et al., 2005; Tassi et al., 2012; Van Dongen, Maislin, Mullington, & Dinges, 2003). Thus, identifying common and distinct aspects of these two kinds of sleep loss may be an important step towards a better understanding of the effects of chronically increased sleep pressure resulting from restricted sleep durations. The first part of the introduction of this thesis provides an overview of the existing scientific evidence for behavioral impairments due to increased sleep pressure resulting from acute SD and chronic SR. The second part focuses on the basic principles of sleep and the regulation of sleep and sleep pressure. The clinical relevance of chronically increased sleep pressure is presented in the third part of the introduction. Finally, the aims of this thesis are presented in the fourth part.

3.1 Behavioral consequences of sleep loss

3.1.1 Behavioral effects of acute SD

So far, acute SD has been intensively applied to study the effects of sleep loss on a variety of cognitive functions (for review see Goel, Rao, Durmer, & Dinges, 2009). Impairing effects have been found for various cognitive domains, however, measures of basic neurobehavioral functioning, such as sustained attention or vigilance, have proven to be among the most sensitive ones to the effects sleep loss (Lim & Dinges, 2010; Lo et al., 2012). Furthermore, impairments of basic neurobehavioral functioning are thought to underlie the impairments in some higher-order cognitive functions (Lim & Dinges, 2010; Lo et al., 2012). Even though acute SD reliably induces dose-dependent, progressively increasing impairments in vigilance for example on a group level (Basner & Dinges, 2011; Lim & Dinges, 2008), there are considerable differences between individuals. Some individuals are highly vulnerable to acute SD and start to show impairments early and reach high levels during the course of SD. In contrast, others show hardly any impairments at all (Van Dongen, Maislin, & Dinges, 2004). Importantly, these differences in vulnerability between individuals have been shown to be highly reliable and stable across time and conditions, i.e., the effects can be reproduced across multiple exposures to acute SD and also occur under different conditions, e.g., differences in prior sleep-wake history (Van Dongen, Baynard, Maislin, & Dinges, 2004). The reproducibility and robustness of the inter-individual differences, thus, qualifies the response to acute SD as a trait (Van Dongen, Vitellaro, & Dinges, 2005). Interestingly though, the trait-like vulnerability does not appear to be the same across different cognitive domains: an individual who is highly vulnerable to present SD induced impairments in one domain, may not show the same extent of vulnerability to impairments in another domain (Van Dongen, Baynard, et al., 2004; Van Dongen, Caldwell, & Caldwell, 2011).

3.1.2 Behavioral effects of chronic SR

While the effects of acute SD have been intensively studied in the past, chronic SR has received far less scientific attention, probably due to time-consuming and costly study designs (e.g., Banks & Dinges, 2007). Early reports and studies found only little adverse effects of chronic SR on cognitive functioning (Blagrove, Alexander, & Horne, 1995; Friedmann et al., 1977; Horne & Wilkinson, 1985; Webb & Agnew, 1974). This led to the assumption that there is a certain amount of "core sleep" of about four to six hours which is needed to maintain functioning and that everything exceeding this amount may be seen as optional sleep (Horne, 1988). However, SR in these studies was often not well controlled (e.g., performed outside the laboratory) and many of these studies lacked statistical power due to small sample sizes or were confounded by other

methodological issues, as for example the assessment of insensitive measures (for detailed discussion see Carskadon & Roth, 1991; Dinges et al., 1997; Van Dongen, Rogers, & Dinges, 2003).

In line with this, more recently, well-controlled laboratory studies showed that chronic SR, indeed, impairs cognitive functioning (Belenky et al., 2003; Dinges et al., 1997; Van Dongen, Maislin, et al., 2003). Two seminal studies showed that impairments in vigilant attention accumulated gradually during the course of chronic SR in a dose-response manner, i.e., the more severely sleep was restricted, the more rapid the impairments accumulated (Belenky et al., 2003; Van Dongen, Maislin, et al., 2003). These findings have been repeatedly replicated and extended since (e.g. Banks, Van Dongen, Maislin, & Dinges, 2010; Lo et al., 2012; Philip et al., 2012; Rupp, Wesensten, & Balkin, 2012; Tassi et al., 2012). As a result, there is now a general consensus that regular sleep durations of less than seven hours per night are associated with impairments in attention, vigilance and working memory in healthy adults (Watson et al., 2015b). However, it is still unclear how chronic SR affects other, especially higher-order cognitive functions. There is some epidemiological evidence that chronic short sleep durations may be linked to alterations in more complex behavior, for example risk-taking (Womack, Hook, Reyna, & Ramos, 2013), however, there is still a lack of laboratory studies systematically investigating the effects of chronic SR on these functions (Watson et al., 2015a).

3.1.3 Comparing the behavioral effects of acute SD and chronic SR

Depending on the amount and duration of chronic SR, basic neurobehavioral impairments, for example in vigilance may reach comparable levels as observed after acute SD: One study that systematically compared these effects reported that restricting time in bed to four hours per night for two weeks resulted in the same level of impairments as did three nights of acute SD (Van Dongen, Maislin, et al., 2003). While this observation was based on a between-subject comparison, it was also shown recently that an individual's vulnerability to develop impairments following sleep loss is preserved between conditions of acute SD and chronic SR (Rupp et al., 2012).

Taken together, one can conclude that vigilant attention is one of the most sensitive and also most investigated behavioral measures influenced by increased sleep pressure. Impairments in vigilance are found after acute SD and chronic SR, with individual differences in vulnerability persisting across these two conditions of sleep loss. Following this overview on behavioral consequences of acutely and chronically increased sleep pressure, basic characteristics of sleep and the regulation of sleep and sleep pressure will be illustrated in the next section.

3.2 Basic characteristics of sleep and sleep regulation

3.2.1 Basic sleep characteristics

The gold-standard to assess and quantify sleep is electroencephalography (EEG) in combination with electrooculography (EOG) and electromyography (EMG) (Berry et al., 2012). Importantly, sleep is not a homogenous behavioral state but consists of different stages which are defined upon distinct characteristics in the EEG, EMG and EOG. Firstly, a major distinction is made between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Carskadon & Dement, 2011). In humans, the former is further subdivided into three sleep stages, i.e., N1, N2 and N3 (Berry et al., 2012). Sleep stage N1 denotes a phase of transition to sleep, normally followed by N2, which is often referred to as the first actual sleep stage. During N2, sleep usually further deepens and eventually results in a transition into sleep stage N3. N3 is also called deep sleep or slow wave sleep as this stage is characterized by low frequency and high amplitude waves in the EEG, referred to as slow waves (Carskadon & Dement, 2011). In contrast to NREM sleep, REM sleep is characterized by a wake-like EEG paralleled by rapid eye movements and muscle atonia (Berry et al., 2012). The different sleep stages occur repeatedly in a cyclic pattern across a sleep episode (Figure 1 top row; Feinberg & Floyd, 1979). During a normal night of sleep, there are typically four to six sleep cycles which on average each last about 90-120 minutes. Earlier cycles usually show larger parts of N3 sleep, while later cycles show larger parts of REM sleep (Carskadon & Dement, 2011).

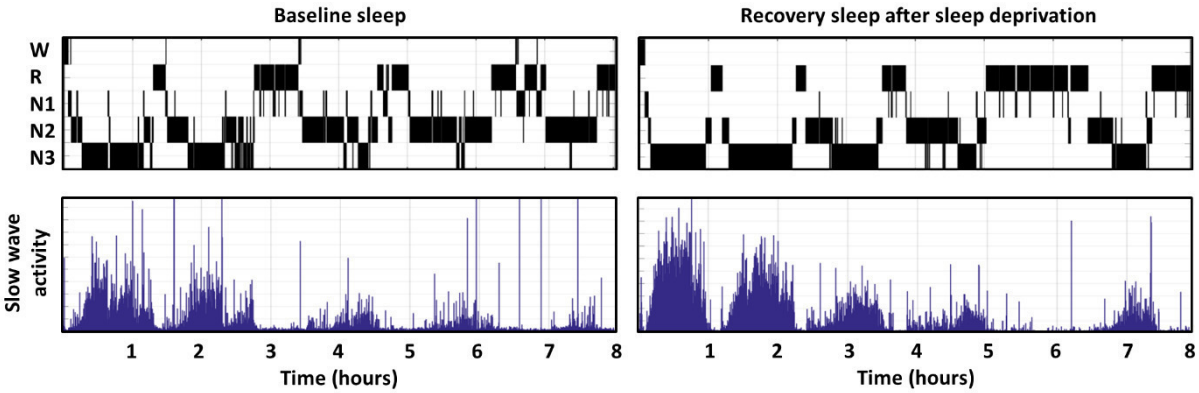

Figure 1 – Top: Sleep stage sequence in a healthy, young adult across 8 hours of nocturnal baseline sleep (left) and recovery sleep after 40 hours of acute sleep deprivation (right). W: wakefulness, R: rapid-eye-movement sleep. Bottom: Slow wave activity (spectral power density between 1-4.5 Hz) across the corresponding nights.

3.2.2 Regulation of sleep and sleep pressure

According to the two-process model of sleep regulation, sleep propensity is regulated by two interacting processes, a homeostatic process S and a circadian process C (for recent review see

Borbély, Daan, Wirz-Justice, & Deboer, 2016). Process C oscillates across a 24-hour cycle and is independent of prior duration of wakefulness. Process S stands for the homeostatic sleep pressure which builds up as a direct function of wakefulness and dissipates as a function of sleep (Achermann & Borbély, 2011). Process S has been shown to be reliably reflected by the quantification of slow waves during NREM sleep, i.e., sleep slow wave activity (SWA), which is the spectral power density in the frequency range of 0.75-4.5 Hz (Borbély, 1982), sometimes also referred to as delta power. Namely, SWA levels have been shown to be highest in the initial parts of a sleep episode and to subsequently decline as sleep proceeds (cf. Figure 1 bottom row; Borbély, Brandeis, Strauch, & Lehmann, 1981; Dijk, Brunner, & Borbély, 1990). Furthermore, the initial levels of SWA change depending on the duration of prior wakefulness (cf. Figure 1 bottom row; Dijk, Beersma, & Daan, 1987; Dijk, Brunner, Beersma, & Borbély, 1990), with increases observed after acute SD (Borbély et al., 1981; Dijk, Brunner, & Borbély, 1990; Dijk, Hayes, & Czeisler, 1993) and decreases observed when naps were taken during the day (Werth, Dijk, Achermann, & Borbély, 1996), i.e., some sleep pressure had already dissipated.

Beyond the mere reflection of homeostatic sleep pressure by SWA, slow waves are also thought to be directly involved in the dissipation of sleep pressure: Selective SWA reduction causes behavioral effects comparable to acute SD (Van Der Werf, Altena, Vis, Koene, & Van Someren, 2011). Furthermore, the extent of SWA increase during recovery sleep following SD has been related to the recovery of cognitive functions (Mander et al., 2010). Hence, as discussed above, changes in initial SWA levels after sleep loss appear to reflect increased sleep pressure which accumulated during previous wakefulness. In contrast, the amount of SWA evident during a whole sleep episode is linked to the restorative function of sleep, i.e., the dissipation of sleep pressure (Achermann & Borbély, 1987; Borbély et al., 1981). Thus, the information obtained by analyzing SWA is different depending on whether one considers the increases in initial levels or the total sum of SWA occurring during a whole sleep period, referred to as slow wave energy (SWE; cf. Plante et al., 2016).

SWA is not equally distributed across the brain, but shows local differences which can be assessed by high-density EEG (Lustenberger & Huber, 2012). In adults, there is typically an anterior to posterior gradient with a frontal predominance of SWA (Figure 2; Ferrara, Gennaro, Curcio, Cristiani, & Bertini, 2002; Riedner et al., 2007; Werth, Achermann, & Borbély, 1996, 1997). Additionally, increases in SWA following acute SD also show local differences, with again frontal areas being more impacted than parietal areas in adults (Cajochen, Foy, & Dijk, 1999; Finelli, Achermann, & Borbély, 2001; Finelli, Borbély, & Achermann, 2001; Marzano, Ferrara, Curcio, & De Gennaro, 2010). Despite this general predominance of frontal SWA increase after

sleep loss, local changes in SWA also occur in a use-dependent manner, with higher SWA in corresponding brain areas following visuo-motor learning (Huber, Ghilardi, Massimini, & Tononi, 2004) or sensory stimulation (Kattler, Dijk, & Borbély, 1994).

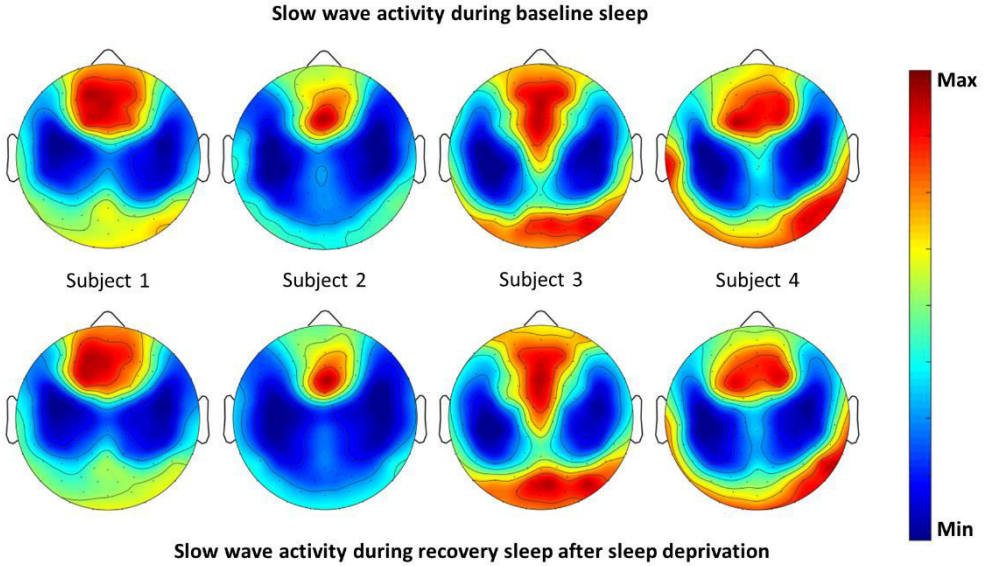

Figure 2 – Slow wave activity (SWA) topographies in four healthy, young adults during baseline (top) and recovery sleep (bottom) following acute sleep deprivation (SD). SWA values are normalized to display minimal (blue) to maximal (red) values across all electrodes in each topography.

While the homeostatic regulation of SWA has been widely studied and confirmed by the condition of acute SD, increases in initial SWA during a recovery night have also been found after chronic SR (Brunner, Dijk, & Borbély, 1993; Plante et al., 2016). These effects were weaker than previously observed after acute SD. An explanation for this observation could be the fact that NREM sleep is prevalent in the first part of sleep (Carskadon & Dement, 2011) and sleep curtailment would therefore result in only a slight restriction of NREM sleep. In contrast, acute SD per definition goes along with a total absence of NREM sleep, thus, resulting in a larger increase of SWA during recovery sleep. Nevertheless, a progressive increase in EEG power of low-frequencies including SWA was observed during the course of chronic SR (Akerstedt, Kecklund, Ingre, Lekander, & Axelsson, 2009).

3.2.3 Individual differences in sleep regulation

SWA measures cannot only be used as a reflection of changes in sleep pressure but can also serve to estimate the individual rate of sleep pressure build-up. Based on SWA increases after acute SD,

sleep pressure build-up rates were found to vary significantly between individuals but to be stable across multiple exposures to acute SD (Rusterholz, Tarokh, Van Dongen, & Achermann, 2016), therefore, also constituting an individual trait. Whether the individual differences in sleep pressure build-up also persist between conditions of acute SD and chronic SR remains unknown.

SWA levels *per se* have been shown to vary strongly between individuals. For example, the individual differences have been reported to be 10-13 times larger than the group-average change induced by SD while the levels are highly stable within individuals (Tucker, Dinges, & Van Dongen, 2007). Furthermore, not only SWA levels but also the topography of SWA varies considerably between individuals (Finelli, Achermann, et al., 2001). These differences have been shown to be rather stable across different conditions: Despite small changes in the overall topography of SWA due to acute SD, the topography remains more similar within the same individual under different conditions (e.g., baseline sleep vs. recovery sleep following SD) compared to between individuals under the same condition (cf. Figure 2; Finelli, Achermann, et al., 2001). Together, this suggests that not only SWA levels but also SWA topographies qualify as traits, similar to the behavioral response to sleep loss (as discussed in section 3.1.1). Considering that SWA is thought to reflect the density of neuronal assemblies (Tononi & Cirelli, 2006), the SWA topography could be a marker for functional anatomical differences (Finelli, Achermann, et al., 2001). Accordingly, studies applying high-density EEG have been able to identify topographical differences linked to healthy development, gender and clinical conditions (Kurth et al., 2010; Ringli, Kurth, Huber, & Jenni, 2013; Ringli, Souissi, et al., 2013; Tesler et al., 2016), potentially reflecting specific aspects of functional neuroanatomy.

Taken together, acutely and chronically increased sleep pressure is reflected by an increase in initial SWA. So far, the basic regulatory mechanisms and their behavioral consequences have been outlined for healthy subjects under laboratory conditions. Next, the clinical relevance of chronically increased sleep pressure will be discussed.

3.3 Clinical significance of chronically increased sleep pressure

3.3.1 The insufficient sleep syndrome

The insufficient sleep syndrome (ISS) is a condition in which clinically relevant symptoms arise due to a persistent failure to obtain sufficient sleep to maintain alertness or stay awake during the day. While excessive daytime sleepiness may occur as a result of a pathological failure to maintain wakefulness, in ISS, it represents a normal homeostatic response to chronic SR (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). Importantly, the insufficient sleep durations are behaviorally induced, i.e., sleep times are restricted by the individual, e.g., because of social or professional duties, while sleep propensity itself is not disturbed or may even be enhanced. As a result, symptoms reverse when the regular sleep duration is extended. Beside the main symptom of excessive daytime sleepiness as a result of chronically increased sleep pressure, other symptoms such as malaise, irritability, anergia, reduced motivation, restlessness, fatigue, dysphoria, uncoordination, or concentration and attention deficits may arise with these secondary symptoms potentially becoming the main focus of the patients. Importantly, the patients often do not notice how much their obtained amount of sleep deviates from the amount they would actually need (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). While the exact factors that contribute to the accuracy of subjective sleep perception are unclear and subjective and objective sleep measures correlate only moderately (Means, Edinger, Glenn, & Fins, 2003), altered sleep perception has been reported in patients with disturbed sleep, as for example insomnia and sleep apnea, compared to healthy controls (Frankel, Coursey, Buchbinder, & Snyder, 1976; McCall, Turpin, Reboussin, Edinger, & Haponik, 1995). Whether sleep perception is also altered in ISS, a condition in which high sleep efficiency parallels short sleep duration, remains unknown.

Studies found that excessive daytime sleepiness is the main complaint of patients seeking advice in sleep disorder clinics (Coleman et al., 1982) and ISS is the cause for sleepiness in about 9% of patients suffering from excessive daytime sleepiness (Komada et al., 2008). The number of individuals with insufficient sleep (but not being diagnosed with ISS) is, however, thought to be even higher (Komada et al., 2008), as short sleep durations are frequently reported in surveys (Groeger et al., 2004; Liu et al., 2016; Tinguely et al., 2014) and those individuals who recognize that their insufficient sleep durations cause their daytime sleepiness may not consult a sleep disorders clinic but may try to individually resolve the issue (Komada et al., 2008).

3.3.2 Differences in sleep need

One difficulty in the identification of insufficient sleep is that sleep need differs strongly between individuals (e.g. Kitamura et al., 2016). Thus, insufficient sleep durations may be difficult to be identified in individuals needing more sleep than the population average (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). Accordingly, not all individuals reporting short sleep durations may suffer from insufficient sleep but some may have a smaller sleep need (Roehrs, Shore, Papineau, Rosenthal, & Roth, 1996). However, some studies found that individuals with habitual short sleep durations are likely to increase total sleep time when time in bed is extended experimentally (Klerman & Dijk, 2005) and most of them show reduced daytime sleepiness as a result (Roehrs et al., 1996). This may indicate that at least some of the individuals reporting habitual short sleep durations are not genuinely having a small sleep need. While genetic variations are thought to contribute to differences in sleep need (de Castro, 2002; Heath, Eaves, Kirk, & Martin, 1998; Partinen, Kaprio, Koskenvuo, Putkonen, & Langinvainio, 1983; Watson, Buchwald, Vitiello, Noonan, & Goldberg, 2010), other factors are also known to influence the amount of sleep needed, as for example health conditions (e.g., Guilleminault & Mondini, 1986; Opp, 2006).

3.3.3 Traumatic brain injury and increased sleep need

One highly prevalent condition, which is increasing worldwide (e.g., Roozenbeek, Maas, & Menon, 2013) and has been linked to increased sleep need, is traumatic brain injury (TBI): A recent meta-analysis showed that about 50% of TBI patients develop sleep-wake disturbances accompanied by increased sleep need and excessive daytime sleepiness being the most frequent complaints (Mathias & Alvaro, 2012). However, most of the studies were conducted retrospectively, used only subjective measures or used inconsistent definitions of sleep-wake disturbances, thus, not allowing the separation of excessive daytime sleepiness and increased sleep need (cf. Sommerauer, Valko, Werth, & Baumann, 2013). Up to now, no prospective, clinical, well-controlled study including objective measures of sleep and sleepiness has been performed to confirm the link between TBI and increased sleep need and potentially chronically increased sleep pressure as a result of not satisfying the higher sleep need.

3.4 Aims

The main aim of this thesis was (i) to assess whether electrophysiological and behavioral correlates of increased sleep pressure resulting from acute SD also apply to the condition of chronic SR. Additionally, we wanted (ii) to investigate potential underlying mechanisms of behavioral changes induced by chronic SR and (iii) to identify aspects of chronically increased sleep pressure in a clinical context. To address these aims, we, on the one hand, conducted a controlled, laboratory, within-subject design study with healthy individuals including the conditions of acute SD and chronic SR and, on the other hand, a controlled, prospective clinical study in a patient population suffering from TBI. The following specific aims were derived and addressed in the corresponding research articles:

1) **To intra-individually compare the homeostatic increase in SWA following acute and chronic sleep loss using high-density EEG and to relate it to impairments in basic neurobehavioral functioning, i.e., vigilance.**
   Rationale: Sleep pressure build-up rates have been shown to vary significantly between individuals and to be stable within an individual across multiple exposures to acute SD (Rusterholz et al., 2016). Up to date, it has not been investigated whether electrophysiological markers of increased sleep pressure, i.e., increases in initial SWA, are individually related across the conditions of acute and chronic sleep loss. It further remains unknown whether the extent of increased sleep pressure as assessed by increased SWA is associated with the individual extent of impairments in basic neurobehavioral functioning, for which vulnerabilities have been shown to persist across the conditions of acute and chronic sleep loss (Rupp et al., 2012). As increases in SWA show topographical differences (Finelli, Achermann, et al., 2001; Finelli, Borbély, et al., 2001; Marzano et al., 2010), we applied high-density EEG to cover the possibility that the examined associations are evident only in distinct brain areas.
   Research article: Intra-individual increase of homeostatic sleep pressure across acute and chronic sleep loss: A high-density EEG study.

2) **To intra-individually assess the effects of acutely and chronically increased sleep pressure on more complex aspects of behavior, i.e., risk-taking behavior, and to explore possible underlying mechanisms of potential behavioral changes.**
   Rationale: While laboratory studies found that chronic SR negatively impacts basic neurobehavioral functioning comparably to acute SD (Van Dongen, Maislin, et al., 2003), the effects of chronic SR on more specific cognitive functions remain unknown.

Epidemiological studies indicate that short regular sleep durations may be linked to increased risk-taking behavior (Womack et al., 2013). However, up to date no study has investigated this link and potential underlying mechanisms experimentally. As slow waves are thought to reflect the restorative function of sleep (Tononi & Cirelli, 2006), we investigated whether local extents of total SWE during the short nights of chronic SR relate to sleep loss induced changes in risk-taking. This would indicate that insufficient restoration of a given brain area may lead to changes in behavior during chronic SR.
Research article: Insufficient sleep: Enhanced risk-seeking relates to low local sleep intensity.

3) **To assess the influence of chronically restricted sleep on the subjective perception of sleep duration.**

Rationale: Patients suffering from ISS often do not notice that the reason for their symptoms are chronically insufficient sleep durations (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). It has been shown that disorders associated with disrupted sleep or the inability to sleep, as for example in sleep apnea or insomnia, are linked to a subjective underestimation of sleep durations (Frankel et al., 1976; McCall et al., 1995). In contrast, it is unknown whether increased sleep continuity due to chronically increased sleep pressure as a result of chronic SR, as it occurs in ISS, results in altered sleep perception and, thus, potentially making the patients overestimating the actual amount of sleep they obtain.
Research article: The impact of sleep restriction and sleep deprivation on subjectively perceived and actigraphically derived sleep parameters.

4) **To prospectively assess the indices of higher sleep need and chronically increased sleep pressure resulting from clinical conditions in the example of TBI.**
Rationale: Sleep need is influenced by clinical conditions (e.g., Guilleminault & Mondini, 1986; Opp, 2006). TBI has been associated with increased sleep need and excessive daytime sleepiness (Mathias & Alvaro, 2012). However, up to date no prospective, controlled study investigated this link by applying objective measures. Furthermore, it is unclear, whether this increased sleep need and excessive daytime sleepiness in TBI patients goes along with electrophysiological markers and sleep architecture characteristics of chronically increased sleep pressure. This may indicate that patients

persistently fail to satisfy their increased sleep need, eventually resulting in excessive daytime sleepiness.

Research article (i): Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial.

Research article (ii): Sleep-wake disorders persist 18 months after traumatic brain injury but remain underrecognized.

4 Research articles

4.1 Intra-individual increase of homeostatic sleep pressure across acute and chronic sleep loss: A high-density EEG study.

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†These authors contributed equally to this work.

Contribution: Experiment design, establishment of methods, data acquisition (including lead in experiment realization), data analysis and writing of the manuscript.

Un-refereed author version. This article has been accepted for publication in SLEEP published by Oxford University Press.

Abstract

Study Objectives: To compare intra-individually the effects of acute sleep deprivation (ASD) and chronic sleep restriction (CSR) on the homeostatic increase in slow wave activity (SWA) and to relate it to impairments in basic cognitive functioning, i.e. vigilance.

Methods: The increase in SWA after ASD (40 hours of wakefulness) and after CSR (7 nights with time in bed restricted to 5 hours per night) relative to baseline sleep was assessed in 9 healthy, male subjects (age = 18-26 y) by high-density electroencephalography (EEG). The SWA increase during the initial part of sleep was compared between the two conditions of sleep loss. The increase in SWA was related to the increase in lapses of vigilance in the psychomotor vigilance task (PVT) during the preceding days.

Results: While ASD induced a stronger increase in initial SWA than CSR, the increase was globally correlated across the two conditions in most electrodes. The increase in initial SWA was positively associated with the increase in PVT lapses.

Conclusions: The individual homeostatic response in SWA is globally preserved across acute and chronic sleep loss, i.e. individuals showing a larger increase after ASD also do so after CSR and vice versa. Furthermore, the increase in SWA is globally correlated to vigilance impairments after sleep loss over both conditions. Thus, the increase in SWA might therefore provide a physiological marker for individual differences in performance impairments after sleep loss.

Keywords: sleep deprivation, sleep restriction, slow wave activity, sleep homeostasis, vigilance.

Statement of Significance

Chronic sleep loss is highly prevalent in modern society. Individuals differ considerably in the extent of performance impairment after sleep loss, and these differences persist across acute and chronic sleep loss. Distinct characteristics in sleep regulatory mechanisms are likely contributing to these differences. An increase in electroencephalography (EEG) slow wave activity (SWA) during initial sleep is a reliable electrophysiological marker of increased sleep pressure. Here we show that individual differences in the increase of SWA are preserved across acute and chronic sleep loss. Furthermore, the increase was found to relate to impairments in vigilance. Thus, the increase in SWA might be a potential marker for individual differences in performance impairments after sleep loss.

Introduction

It is well-known that acute sleep deprivation (ASD), i.e. a one-time prolongation of wakefulness, negatively impacts a variety of cognitive functions (Goel et al., 2009; Lim & Dinges, 2010). While strong effects are consistently found for simple attention and vigilance tasks on a group-level (Lim & Dinges, 2010), large inter-individual differences exist in the extent of these effects. In fact, these differences range from almost resistant to highly vulnerable subjects and persist within subjects across repeated exposure to ASD (e.g., Van Dongen, Maislin, et al., 2004). Recently an increasing body of research focuses on the effects of chronic sleep restriction (CSR), a condition of repeated partial sleep loss. The major reason for the growing interest in CSR is that it resembles everyday sleep loss much more than ASD, as more individuals in our society suffer from chronically inadequate sleep durations than from ASD (Banks & Dinges, 2007; Basner et al., 2013; Krueger & Friedman, 2009). CSR, depending on the duration and extent of sleep restriction, has been shown to lead to comparable impairments in vigilance, working memory and cognitive throughput as ASD (Van Dongen, Maislin, et al., 2003). Interestingly, across both ASD and CSR, an individual's vulnerability to develop impairments following sleep loss persists (Rupp et al., 2012).

On the electrophysiological level, slow wave activity (SWA) during non-rapid eye movement (NREM) sleep, i.e., the EEG spectral power between 0.5-4.5 Hz (Borbély et al., 1981), is an established marker of increased sleep pressure due to prolonged wakefulness. More specifically, we know from numerous ASD studies that the initial level of SWA (i.e., during initial parts of a sleep episode) increases as a function of the duration of prior wakefulness (e.g., Borbély et al., 1981; Dijk et al., 1987; Dijk, Brunner, Beersma, et al., 1990). In the course of sleep, SWA decreases reflecting the recovery function of sleep (Achermann & Borbély, 1987; Borbély et al., 1981). It has recently been shown, that the sleep pressure build-up during wakefulness and its dissipation during sleep vary independently across individuals, thus, displaying distinct dynamics (Rusterholz et al., 2016). In addition to the higher initial level of SWA after ASD, there is also a faster dynamic of SWA build-up during the beginning of a sleep episode after ASD (Borbély et al., 1981; Dijk, Brunner, Beersma, et al., 1990). Furthermore, EEG recordings using a large number of electrodes revealed regional differences in the SWA increase after ASD, with frontal regions showing most pronounced effects (Finelli, Achermann, et al., 2001; Finelli, Borbély, et al., 2001; Marzano et al., 2010). Regional differences also exist in the dynamics of sleep pressure build-up across the cortex (Rusterholz & Achermann, 2011; Zavada, Strijkstra, Boerema, Daan, & Beersma, 2009). Thus, when estimating the dynamics of the sleep pressure build-up based on

ASD data, not only differences between cortical areas but also between subjects were found (Rusterholz & Achermann, 2011).

Some studies further investigated the changes in SWA during and following CSR. A less consistent picture emerges because the magnitudes of the SWA increase seemed to depend on the time-window in which SWA was assessed (Akerstedt et al., 2009; Brunner et al., 1993; Plante et al., 2016). More precisely, increases in SWA during CSR were only evident when compared to SWA during an equivalent time window during baseline sleep (i.e., not to the whole baseline night; Akerstedt et al., 2009; Plante et al., 2016). Additionally, increases in SWA during recovery sleep following CSR have only been found for the first half of the sleep period (i.e., about first 4 hours), not for the second half (Brunner et al., 1993). Furthermore, the faster build-up of SWA was more pronounced during the first sleep cycle compared to later ones (Brunner et al., 1993).

It has been shown that between-subject differences in sleep pressure build-up rates, assessed in one central derivation, are stable across repeated exposure to ASD (Rusterholz & Achermann, 2011). However, no study investigated up to date whether the magnitude of the sleep pressure increase, reflected by increased initial SWA, is related in the same individuals undergoing ASD and CSR. In other words, it is unknown whether an individual showing a relatively large increase in initial SWA after ASD also shows a relatively large increase after CSR and whether such an agreement would exist across all cortical areas. Our aim was therefore to assess whether an individual's homeostatic response to sleep loss is 1) preserved between ASD and CSR and 2) consistent across cortical areas and 3) related to classical behavioral markers of increased sleep pressure, i.e., vigilance impairments.

Methods

Study Design

The study was conducted in the sleep laboratory at the Department of Neurology of the University Hospital Zurich and comprised an ASD condition of 40 hours of continuous wakefulness and a CSR condition consisting of seven consecutive nights with time in bed restricted to five hours per night. Subjects underwent both conditions in a counter-balanced order and times in the protocol were adjusted to individual habitual bedtimes. Both conditions were separated by at least two weeks and were preceded by one week of regular sleep-wake rhythm with time in bed fixed to eight hours per night, which was controlled by wrist-actigraphy (on the non-dominant wrist; light sensor data included, ActiWatch, Respironics; Morgenthaler et al., 2007) and sleep diaries. The ASD was performed in the laboratory under constant supervision. The CSR was achieved by

delaying the individual bedtime by two hours and advancing the wake-up time by one hour. The subjects spent the first four nights of CSR at home and the last three nights in the sleep laboratory. During the times at home, compliance to restricted time in bed was controlled by actigraphy, sleep diaries and phone calls. Here we compared baseline sleep (assessed at the beginning of the protocol) to recovery sleep following 40 hours of ASD and to sleep following seven nights of CSR. Bedtimes were kept constant during baseline and recovery nights and time in bed was fixed to eight hours. Vigilance was assessed every three hours, starting one hour after habitual wake-up time until three hours prior to habitual bedtime (five assessments per condition in total), during the day following the baseline sleep assessment, after the night of ASD and after the seventh night of CSR.

The study was approved by the local ethics committee and all subjects gave written informed consent.

Subjects

Data presented in the current manuscript constitute a subpart of the complete data set, i.e., nine of the totally 14 subjects undergoing this study were included in the analysis, as no sleep recordings after completion of CSR were available in the other five subjects. The subjects were 18-26 years old (mean ± s.d.: 21.2 ± 2.4 years) and reported regular sleep durations of seven to eight hours per night (7.6 ± 0.4 hours). All of them were male, right-handed, in good general health, reported no regular medication intake, excessive caffeine consumption or drug or alcohol abuse, were non-smoking, did not work shifts, did not travel across more than two time zones for at least one month prior to study participation and reported no sleep complaints or excessive daytime sleepiness (according to the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the Epworth Sleepiness Scale (Johns, 1991)). A screening night in the sleep laboratory was performed to exclude any undiagnosed sleep disorders (e.g. sleep apnea or periodic leg movements), to ensure subjects had sufficiently high sleep efficiency (> 80%) and to let the subjects adapt to the laboratory environment and EEG equipment.

Subjects had to refrain from caffeine, alcohol and any medications starting three days prior to and throughout the ASD and CSR protocols. Furthermore, no food and drinks (except water) were allowed 30 minutes prior to any sleep or behavioral recordings. To avoid excessive sweating or heating, no extensive exercises or sauna were allowed on days with recordings.

Sleep EEG Recordings and Spectral Analysis

Because the increase in SWA after sleep loss has previously been reported to display regional differences (Cajochen et al., 1999; Finelli, Achermann, et al., 2001; Finelli, Borbély, et al., 2001; Marzano et al., 2010), sleep was recorded by high-density EEG nets consisting of 128 electrodes (Electrical Geodesics Inc. Sensor Net for long-term monitoring) including electrooculogram and electromyogram. The net was applied and adjusted to the vertex (Cz) right before bedtime and electrode impedances were kept below 50 kΩ. Sleep was recorded throughout the time in bed with a sampling rate of 500 Hz. Offline processing was conducted in Matlab (The Mathworks, Inc.). In accordance with previous studies (e.g., Wilhelm et al., 2014), the processing included data filtering (0.5 Hz high-pass, 40 Hz low-pass), down-sampling to 128 Hz, visual sleep stage scoring based on 20-second epochs according to standard criteria (Berry et al., 2012), visual and semi-automatic rejection of artifactual epochs (cf. Lustenberger, Wehrle, Tüshaus, Achermann, & Huber, 2015), rejection of poor-quality channels and exclusion of channels below the ears (to avoid artifacts induced by facial and neck muscles) and re-referencing of the data to the mean of all un-rejected channels.

Sleep cycles were defined according to the criteria of Feinberg and Floyd (1979). In one subject the first sleep cycle was markedly prolonged and displayed two clear SWA peaks separated by a trough in one night (baseline) in comparison to other nights and cycles in this subject. Such a phenomenon has previously been described as a failure to visually detect REM sleep in the first sleep cycle (Feinberg & March, 1988). Thus, according to previous studies the first NREM episode was defined to last only up to the trough of SWA in this case (e.g., Khatami et al., 2008; Tarokh, Carskadon, & Achermann, 2012). This subject was not included in the calculation and comparison of REM sleep latencies.

SWA for all artifact-free N2 and N3 epochs was calculated in each electrode as the mean spectral power in the range of 1 – 4.5 Hz (Fast Fourier Transform routine, Hanning window, averages of five 4 second epochs). SWA of previously rejected channels due to bad quality were interpolated using a spherical interpolation (Delorme & Makeig, 2004), resulting in SWA data of 109 channels in each subject and condition (without the electrodes below the ears). The time point of maximal SWA averaged over all electrodes was determined based on 2-min intervals (SWA average over 6 consecutive 20-second epochs), i.e., the time point of maximal SWA was defined as the 2-min interval with highest global SWA.

Increases in SWA were always calculated as percentage change to the corresponding baseline level.

Assessment of Vigilance

Vigilance was measured using the psychomotor vigilance task (PVT; PVT-192, Ambulatory Monitoring Inc.; Dinges & Powell, 1985), a sustained visual vigilance reaction time task. Lapses (i.e. count of reaction times > 500 ms) in the PVT have been shown to be sensitive to the condition of ASD and CSR (Basner & Dinges, 2011). Furthermore, a trait-like vulnerability for the increase in PVT lapses has been shown to persist across ASD and CSR (Rupp et al., 2012). We transformed the number of lapses (x) by $\sqrt{x} + \sqrt{(x+1)}$ to approximate normal distribution of the data (cf. Dinges et al., 1997). We than averaged the values across all five assessments per condition (baseline, ASD, CSR) in line with previous studies (Banks et al., 2010; Rupp et al., 2012; Van Dongen, Maislin, et al., 2003). Increases in lapses were calculated as the difference between baseline values and values during ASD and CSR, respectively.

Statistics

All statistical tests and corresponding figures were realized in Matlab or R (R Development Core Team, 2009). SWA between conditions and the difference in SWA increase after ASD and CSR were compared electrode-wise by paired-samples t-tests. Associations between SWA increases after ASD and CSR and the association of SWA increase and the increase in PVT lapses was assessed by Pearson's correlation coefficients. To control for multiple comparisons, we performed non-parametric statistical mapping (SnPM) with suprathreshold cluster testing (Nichols & Holmes, 2002) as previously applied in high-density EEG studies (Huber et al., 2006; C. Lustenberger et al., 2015; Plante et al., 2016). To assess the mean ± s.e.m across correlation coefficients in a significant cluster, Fisher's z-transform was applied to every correlation coefficient before averaging. The obtained averages were transformed back afterwards.

For the correlation between the SWA increase and the increase in PVT lapses we pooled the data obtained during ASD and CSR in order to increase statistical power and to assess the association across both conditions. To exclude that mainly differences between subjects drive any correlation (as every subject contributed two data points to the correlation), we further performed a mixed model analysis in which the random factor subject was included in a linear model predicting the increase in PVT lapses by the increase in SWA. We tested whether including the random factor subject significantly increased the model fit - i.e., whether the random factor should be included in the model or not - by comparing the deviance of the models with a χ^2-Test. Of the electrodes showing a significant association between SWA increase and increase in lapses, only five electrodes displayed a significant increase in model fit by including the random factor subject.

The association between SWA increase and increase in lapses remained significant in all but one electrode when performing the mixed model analysis. Hence, Pearson's correlation coefficients are reported in the results, to stay consistent over all electrodes. Nevertheless, we would like to note that performing this analysis despite the lack of improved model fit in the majority of electrodes (102 out of 109), resulted in a very similar pattern of significant association between SWA increase and increase in PVT lapses (data not shown).

Additionally, to exclude that mere level differences between ASD and CSR would drive any correlation, we assessed the increase in adjusted explained variance when including the factor condition (ASD vs. CSR) as a second predictor for the increase in PVT lapses predicted by SWA increase in a linear model by the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Including the factor condition did not improve the model fit in any of the electrodes displaying a significant association between SWA increase and increase in lapses. Furthermore, the effect of the factor condition was not significant in any electrode when included anyway as a second predictor (data not shown).

Results

Increased sleep efficiency and duration of deep sleep on the one hand and decreased sleep latency and shorter duration of lighter sleep stages (N1 and N2) on the other hand were found after ASD as expected due to the elevated sleep pressure. The changes in the variables after the CSR condition were similar but smaller in their extent (Table 1). REM sleep latency was decreased after ASD and CSR, while REM sleep duration only increased significantly after CSR (Table 1). Compared to both baseline and ASD, the first NREM sleep episode was markedly shorter after CSR (Table 2). Within this first NREM episode N1 and N2 duration were decreased after ASD and CSR and N3 duration was decreased after CSR only (Table 2), probably due to the shortened duration of the first NREM episode after CSR. Sleep efficiency was high in all three nights (Table 1), indicating that sleep was not disturbed by wearing hd-EEG nets.

Sleep loss is known to increase SWA especially during the initial part of sleep (Borbély et al., 1981; Dijk, Brunner, & Borbély, 1990). Variable time windows can be used to investigate this period. In a first step, we chose a time window assessing the same number of epochs in every subject, i.e., the first hour of artifact-free N2 and N3 epochs. When using this time window, SWA topographies revealed a typical spatial pattern with maximal values over frontal regions in all three conditions (baseline, after ASD and after CSR; data not shown). We then contrasted the prolonged wakefulness conditions (ASD and CSR) to the baseline. Compared to baseline, SWA

values during the first hour of NREM sleep were significantly increased in all electrodes after ASD (Figure 1A; mean increase over all electrodes ± s.e.m: +42.4 ± 6.3 %, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing). In contrast, there was no significant increase in any electrode found after CSR (Figure 1A; mean increase over all electrodes: +2.5 ± 4.1%). This result, however, might be biased due to significantly reduced duration of the first NREM sleep episode after CSR (cf. Table 2): the first NREM episode was on average shorter than one hour after CSR whereas it was longer than one hour at baseline and after ASD. Individual data analyses revealed that indeed SWA of the first hour of N2 and N3 included exclusively epochs from the first NREM episode in 8 out of 9 subjects at baseline, but only in 2 out of 9 subjects after CSR. Hence, in 6 subjects the SWA values included an additional phase of SWA build-up during the second NREM episode after CSR but not at baseline.

Table 1 All-night sleep characteristics.

	Means (± s.e.m.)			Paired-samples t-test (two-sided)		
Variable	BL	ASD	CSR	BL vs. ASD	BL vs. CSR	ASD vs. CSR
Sleep latency (min)	11.7 (± 1.8)	3.9 (± 0.7)	11.4 (± 2.8)	T(8) = -3.86 **P = 0.005**	T(8) = 0.11 P = 0.914	T(8) = -2.59 **P = 0.032**
N1 (min)	36.2 (± 3.6)	14.9 (± 1.7)	25.4 (± 3.8)	T(8) = 7.27 **P = 0.000**	T(8) = 4.19 **P = 0.003**	T(8) = -3.46 **P = 0.009**
N2 (min)	196.3 (± 8.0)	172.8 (± 10.4)	175.0 (± 5.8)	T(8) = 1.73 P = 0.122	T(8) = 3.65 **P = 0.007**	T(8) = -0.24 P = 0.815
N3 (min)	112.9 (± 5.7)	165.8 (± 8.3)	127.1 (± 7.4)	T(8) = -6.47 **P = 0.000**	T(8) = -2.15 P = 0.063	T(8) = 6.94 **P = 0.000**
REMS (min)	107.0 (± 4.1)	116.1 (± 8.2)	129.3 (± 6.4)	T(8) = -1.12 P = 0.296	T(8) = -2.91 **P = 0.020**	T(8) = -1.54 P = 0.162
WASO (min)	16.1 (± 4.1)	6.7 (± 1.9)	11.9 (± 5.0)	T(8) = 2.22 P = 0.057	T(8) = 0.65 P = 0.532	T(8) = -1.51 P = 0.169
Sleep efficiency (%)	94.3 (± 1.0)	97.8 (± 0.4)	95.2 (± 1.1)	T(8) = -3.27 **P = 0.011**	T(8) = -0.79 P = 0.454	T(8) = 3.24 **P = 0.012**
N3 latency (min)	9.4 (± 0.7)	3.2 (± 0.3)	6.6 (± 1.0)	T(8) = 7.26 **P = 0.000**	T(8) = 2.65 **P = 0.029**	T(8) = -3.53 **P = 0.008**
REMS latency (min)	79.5 (± 5.8)	64.1 (± 4.4)	55.7 (± 3.2)	T(7) = 3.22 **P = 0.015**	T(7) = 3.68 **P = 0.008**	T(7) = 1.85 P = 0.107

BL: baseline sleep, ASD: sleep following acute sleep deprivation, CSR: sleep following chronic sleep restriction, REMS: rapid-eye-movement sleep, N1-3: non-REM sleep stages, WASO: wake after sleep onset. Sleep latency was defined as the first occurrence of N2. REMS and N3 latency was defined as the time between sleep onset and the first occurrence of REMS or N3, respectively. Sleep efficiency was defined as time asleep in relation to time in bed. Bold P-values highlight significant differences.

Table 2 First NREM sleep episode characteristics.

	Means (± s.e.m.)			Paired-samples t-test (two-sided)		
Variable	BL	ASD	CSR	BL vs. ASD	BL vs. CSR	ASD vs. CSR
Episode duration (min)	79.1 (± 5.2)	70.0 (± 7.0)	55.7 (± 2.8)	T(8) = 1.21 P = 0.260	T(8) = 4.09 **P = 0.004**	T(8) = 2.01 P = 0.080
N1 (min)	2.3 (± 0.4)	0.3 (± 0.1)	0.9 (± 0.2)	T(8) = 4.66 **P = 0.002**	T(8) = 2.75 **P = 0.025**	T(8) = -2.78 **P = 0.024**
N2 (min)	18 (± 2.8)	8.4 (± 0.9)	11.3 (± 1.0)	T(8) = 4.12 **P = 0.003**	T(8) = 2.51 **P = 0.036**	T(8) = -2.46 **P = 0.039**
N3 (min)	57.4 (± 3.1)	61.0 (± 6.1)	43.3 (± 2.7)	T(8) = -0.58 P = 0.581	T(8) = 4.07 **P = 0.004**	T(8) = 2.71 **P = 0.027**
Wake (min)	0.6 (± 0.3)	0.3 (± 0.1)	0.3 (± 0.1)	T(8) = 1.03 P = 0.334	T(8) = 0.96 P = 0.366	T(8) = 0.17 P = 0.870
Analyzed epochs (#)	210.1 (± 14.9)	195.7 (± 20.1)	152.3 (± 7.8)	T(8) = 0.63 P = 0.543	T(8) = 3.32 **P = 0.011**	T(8) = 2.23 P = 0.056
2-min epochs up to max. SWA (#)	19.6 (± 2.7)	16.4 (± 2.0)	17.6 (± 1.4)	T(8) = 1.05 P = 0.662	T(8) = 0.63 P = 0.547	T(8) = 0.33 P = 0.527

BL: baseline sleep, ASD: sleep following acute sleep deprivation, CSR: sleep following chronic sleep restriction, NREM: non-rapid eye movement sleep, SWA: Slow wave activity. Analyzed epochs correspond to all artifact-free 20-second N2 and N3 epochs. 2-min epochs up to max. SWA correspond to the number of 2-min epochs up to the 2-min epoch with globally highest SWA values within the first NREM episode. Bold P-values highlight significant differences.

Facing these differences in NREM episode duration, we next assessed SWA during the entire first NREM episode only. Indeed, it has been previously noted that a sleep cycle constitutes a physiological meaningful time range to assess SWA (Dijk, Brunner, & Borbély, 1990; Feinberg, Floyd, & March, 1987), as it takes the structure of sleep into account. Following ASD, SWA during the first NREM episode was again increased in all electrodes compared to baseline (Figure 1B; mean increase over all electrodes: +46.0 ± 5.5 %, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing) but also after CSR in a cluster of 20 electrodes over left centro-parietal and temporal regions (Figure 1B; mean increase in cluster electrodes: +18.5 ± 4.2 %, cluster size: $P < 0.05$, SnPM suprathreshold cluster testing; mean increase over all electrodes: +15.3 ± 4.1 %).

Sleep loss strongly affects the initial build-up of SWA, i.e., SWA not only reaches higher levels but also increases faster, reflecting the increase in sleep pressure during preceding prolonged wakefulness (Brunner et al., 1993; Dijk, Brunner, & Borbély, 1990; Dijk et al., 1993). According to the two-process model of sleep regulation, the build-up of sleep pressure is reflected by the

asymptotic level SWA reaches within a sleep cycle. In contrast, the decrease in SWA during the course of sleep reflects the dissipation of sleep pressure (Achermann & Borbély, 2011). To account for these SWA dynamics, we assessed in a next step SWA from the onset of sleep up to the maximal level reached during the first cycle in every condition and for every individual separately. With this procedure we aimed at maximally separating the two aspects SWA levels are reflecting, i.e., 1) the accumulated sleep pressure during preceding wakefulness reflected in the initial levels and 2) the dissipation of sleep pressure reflected in the decreasing levels across sleep. Comparing SWA during this initial SWA build-up period revealed again a similar picture when comparing ASD to baseline, with all electrodes showing a significant and even more pronounced increase in SWA (Figure 1C, mean increase over all electrodes: +60.2 ± 8.7 %, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing). After CSR, SWA during this time period was significantly increased in two large clusters of electrodes, i.e. 32 electrodes over fronto-cental regions and 26 electrodes over occipito-temporal regions (Figure 1C, mean increase over fronto-central cluster: +25.9 ± 9.5 %; over occipito-temporal cluster: +23.3 ± 8.3%, both cluster sizes: $P < 0.05$, SnPM suprathreshold cluster testing). As this measure of SWA increase displayed the spatial pattern typically reported in previous sleep loss studies (cf. Finelli, Borbély, et al., 2001) and showed a notable increase in both conditions of sleep loss, we continued our analysis with the increase in SWA during the initial build-up period.

Next, we directly compared the two sleep loss conditions and found that the increase in SWA during the initial build-up period was more pronounced after ASD than after CSR in all electrodes (Figure 2A, average difference of increase after ASD compared to after CSR over all electrodes: +38.48 ± 4.6%, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing). This difference fits well to the observed changes in sleep architecture also indicating a larger increase in the level of sleep pressure after ASD than CSR (cf. Table 1). To assess whether subjects showing a relatively large increase in one condition did so also in the other condition and vice versa, we correlated the increase after ASD and CSR. We found that the increase in one condition was significantly correlated with the increase in the other condition in 90 electrodes forming a widespread pattern of positive associations (Figure 2B and 2C, mean r over these electrodes: 0.83 ± 0.02, cluster size: $P < 0.05$, SnPM suprathreshold cluster testing). Hence, while ASD introduced a stronger increase in sleep pressure compared to CSR, subjects responding to ASD with a large response did so in the CSR condition too.

Finally, we assessed whether the increase in SWA during the initial build-up period relates to the neurobehavioral impairments that occurred during preceding wakefulness. To do so we correlated the increase in SWA during the initial build-up period after both sleep loss conditions with the

increase in PVT lapses and found a rather global, widespread positive association in 76 electrodes between these two measures (Figure 3, mean *r* over these electrodes: 0.62 ± 0.02, cluster size: P < 0.05, SnPM suprathreshold cluster testing). The pattern of the association was similar for both sleep loss conditions separately (data not shown) and was not driven by the inclusion of multiple (i.e., 2) data points per subject or by mere level differences between conditions, as controlling for these factors did not significantly change the association (see methods for details).

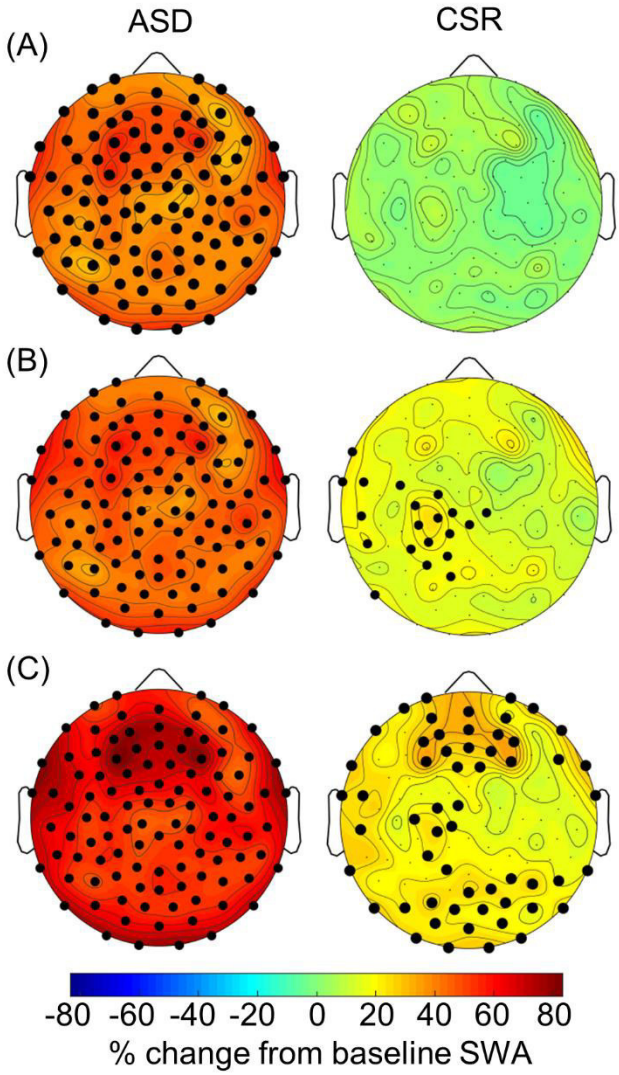

Figure 1 - Topographical distribution of slow wave activity (SWA) increase relative to baseline after acute sleep deprivation (ASD) and chronic sleep restriction (CSR). White dots indicate electrodes with a significant increase compared to baseline (P < 0.05, SnPM suprathreshold cluster testing). (A) SWA increase during the first hour of N2 and N3 sleep. (B) SWA increase during the first NREM episode. (C) SWA increase during the initial build-up phase of SWA.

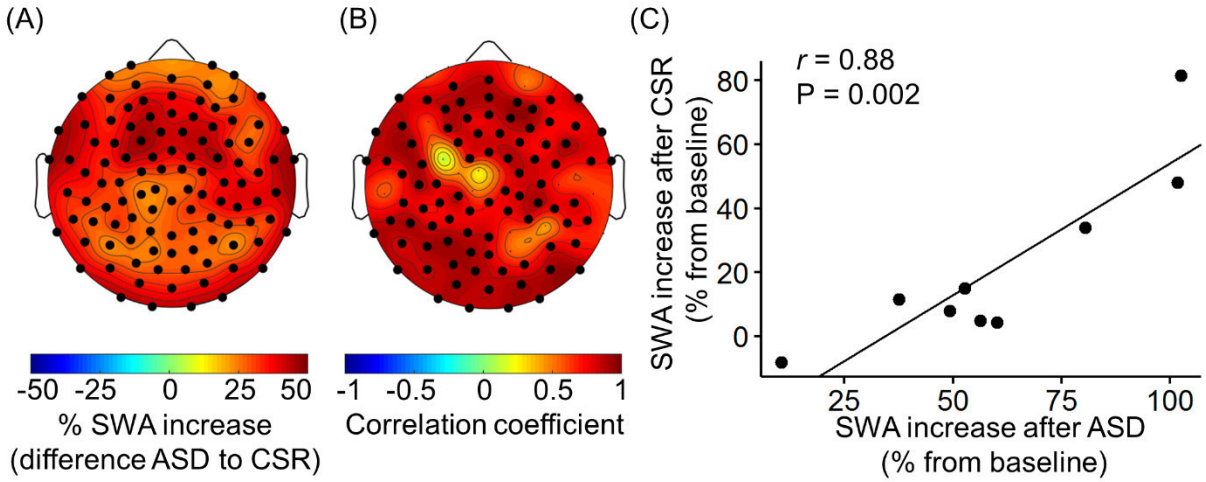

Figure 2 - Difference and correlation of slow wave activity (SWA) increase after acute sleep deprivation (ASD) and after chronic sleep restriction (CSR) relative to baseline. Black bold dots indicate significant electrodes ($P < 0.05$, SnPM suprathreshold cluster testing). (A) Topographical distribution of differences (% increase above baseline after ASD minus % increase above baseline after CSR). (B) Topographical distribution of Pearson's correlation coefficients for the association between the increase in SWA after ASD and the increase after CSR. (C) Association between average SWA increase over all significant electrodes in B (Pearson's correlation coefficient).

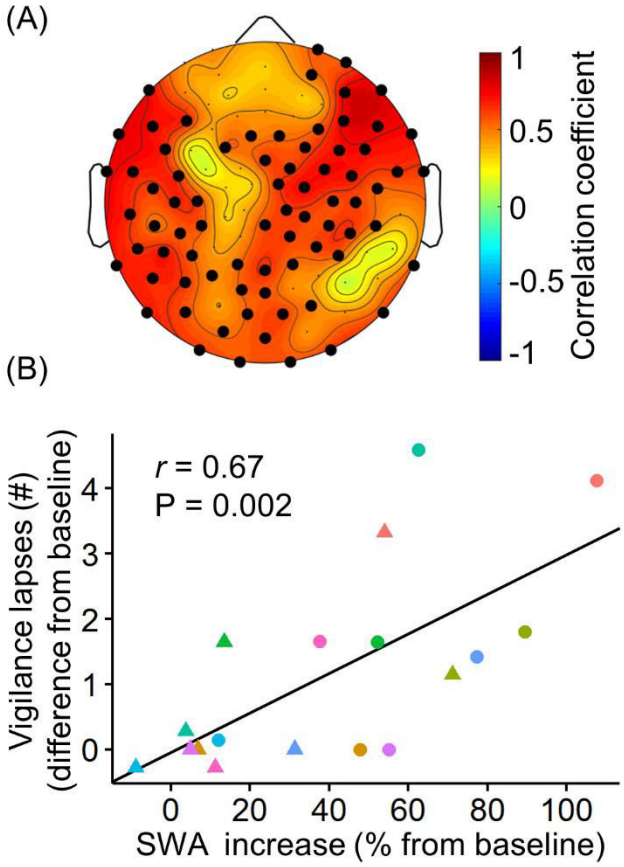

Figure 3 - Correlation of slow wave activity (SWA) increase and increase in vigilance lapses. (A) Topographical distribution of Pearson's correlation coefficients. White dots indicate significant electrodes ($P < 0.05$, SnPM suprathreshold cluster testing). Data was merged for the acute sleep deprivation (ASD) and the chronic sleep restriction (CSR) conditions (see methods for details). (B) Association between the increase in vigilance lapses and the average SWA increase over all significant electrodes in A (Pearson's correlation coefficient). Colors indicate data points of the same individual. Circles mark data for ASD and triangles for CSR.

Discussion

The individual homeostatic increase in sleep pressure, as reflected by the increase in SWA, of two sleep loss conditions was related in almost all electrodes over the scalp. Previously it has been shown that SWA levels per se (Tucker et al., 2007) and the SWA topography (Finelli, Achermann, et al., 2001), show trait-like characteristics across baseline conditions and ASD. Also parameter estimations quantifying the dynamics of sleep pressure build-up have been shown to be trait-like across repeated ASD in the same individuals (Rusterholz et al., 2016). Our results add to these findings indicating that also the change in SWA induced by homeostatic challenges is preserved within an individual across different conditions of sleep loss.

Interestingly, it has been shown that an individual with relatively large neurobehavioral impairments after ASD does so also after CSR (Rupp et al., 2012). Thus, we assessed the relationship with PVT lapses. The positive relationship between the SWA increase and the increase in PVT lapses was rather widespread but varied in its extent across cortical areas. We acknowledge that a lack of significant correlations in some areas might be the result of low power considering the small sample size. However, the lack of a strong association in frontal electrodes seems surprising at first glance as the frontal cortex has been shown to respond particularly strong to sleep loss (Cajochen et al., 1999; Finelli, Achermann, et al., 2001; Finelli, Borbély, et al., 2001; Marzano et al., 2010). This unexpected finding could potentially be explained by compensatory mechanisms as for example a higher activation following sleep loss in some frontal areas that has been linked to less drowsiness (Poudel, Innes, & Jones, 2012). Since SWA has been shown to locally increase in a use-dependent manner (Goel, Abe, Braun, & Dinges, 2014; Huber et al., 2004; Hung et al., 2013; Kattler et al., 1994), less vulnerable subjects showing compensation-related higher activity in frontal areas could be expected to display a further, potentially un-proportional increase in frontal SWA. As a result, we would not expect a linear but a more complex relationship between SWA increase and behavioral impairments in areas being recruited successfully in a compensatory manner.

Up to date, it is still largely unclear which factors exactly contribute to individual differences in the vulnerability to sleep loss induced cognitive impairments (Van Dongen, Caldwell, et al., 2011). It has been suggested that impairments result from repetitive use of distinct neuronal groups involved in a given cognitive process which as a result fail to function due to emerging local restoration need. Furthermore, individuals are thought to differ in the extent they are vulnerable to such use-dependent effects in specific neuronal groups (Van Dongen, 2012; Van Dongen, Belenky, & Krueger, 2011). One could speculate that the local extent of increased SWA at the beginning of sleep reflects such a vulnerability. Moreover, also local use-dependent increases of SWA on top of the global increase were observed after prolonged wakefulness (Goel et al., 2014; Hung et al., 2013). The rather wide-spread than local association we found between the increase in SWA and the increase in PVT lapses fits to the notion that not only one specific cortical area is thought to be responsible for lapsing (Lim & Dinges, 2008). Nevertheless, performance in other cognitive tasks might depend differently on distinct brain areas. Estimations of sleep pressure build-up rates based on ASD data display distinct spatial patterns and vary significantly between individuals (Rusterholz & Achermann, 2011). This further indicates that such spatial differences might be an underlying mechanism of differential individual vulnerabilities to sleep loss impairments across different cognitive processes (Frey, Badia, & Wright, 2004; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010; Van Dongen, Baynard,

et al., 2004; Van Dongen, Caldwell, et al., 2011). Hence, it seems reasonable that the relationship between increased SWA and impairments in more specific cognitive processes would display spatially more restricted associations which could be assessed by high-density EEG. However, this remains speculative and requests further investigation.

A major limitation in our study is certainly the small number of subjects, which might have caused some power issues in statistical analysis. Furthermore, we cannot exclude that the findings are restricted to young, healthy male subjects with habitual sleep times of 7-8 hours. Thus, the findings should be replicated in a larger and more heterogeneous population. Because we only assessed SWA after the completion of CSR, we cannot make any assumptions about the time course or dose-response of the SWA increase during CSR. As our study was not designed to address this aspect, future studies, including the assessment of the SWA increase during the whole course of CSR could therefore provide additional information on that issue.

Our analysis revealed that the time window in which SWA is assessed might be important when investigating the effects of CSR. The observed changes in sleep structure, i.e. changed duration of the first NREM episode and duration of N3 in the first NREM episode, might lead to a bias in SWA values between different conditions when a fixed time window is analyzed. Assessing and dealing with such changes in dynamics seems especially important in the condition of CSR. One reason for this could be the lower extent of sleep pressure increase after CSR, given the duration and extent with which it was realized in this study. A lower increase might be more sensitive to biases. Another reason for the stronger bias in CSR outcome measures could be the observed increase in REM sleep pressure as reflected by the significant increase in REM sleep duration and the decrease in REM sleep latency, which has previously been reported to occur after CSR (Akerstedt et al., 2009; Brunner et al., 1993; Carskadon & Dement, 1981; Goel et al., 2014; Plante et al., 2016). The increased REM sleep pressure after CSR could interact with the increased NREM sleep pressure, causing the first NREM sleep episode to be shorter, similar to the observation of sleep onset REM in individuals with chronically insufficient sleep durations (Carskadon & Dement, 2011). Furthermore, simulation studies have shown previously that differences in REM sleep latencies consequently result in differences in SWA values of the first NREM episode (Beersma & Achermann, 1995). Thus, we believe that the most unbiased measure in our case was SWA during the initial build-up period, as it is not primarily influenced by shorter NREM episode durations per se. This was also evident, when comparing the number of epochs included in the analysis, which was significantly different between conditions when the whole first NREM episode was analyzed, but not when analyzing SWA during the initial build-up period up to the maximal 2-min epoch (cf. Table 2). Additionally, we have chosen this time-window, as

the initial level of SWA is thought to reflect the accumulated sleep pressure during preceding wakefulness on the one hand (Borbély et al., 1981; Dijk et al., 1987) and is also thought to be functionally involved in the dissipation of sleep pressure across the night on the other hand (Tononi & Cirelli, 2006). The processes of sleep pressure build-up during wakefulness and of sleep pressure dissipation during sleep have been shown to be independent, i.e., not related within an individual (Rusterholz et al., 2016). Hence, larger time windows, not taking into account the dynamics of SWA and therefore also including times of declining SWA, as it occurs within and across consecutive sleep cycles (Borbély et al., 1981; Brunner et al., 1993; Dijk, Brunner, & Borbély, 1990), might represent a mixture of these processes and result in SWA values not adequately reflecting the level of increased sleep pressure resulting from preceding wakefulness.

Conclusion

We show here, that the individual extent in homeostatic response as measured by the SWA increase is related across chronic and acute sleep loss. This relationship was not limited to certain brain areas but evident in a widespread pattern all over the cortex. Furthermore, the SWA increase was associated with impairments in vigilance over both conditions and might therefore provide a physiological marker for individual differences in performance impairments after sleep loss. This might be an important step towards a better understanding of mechanisms underlying the individual vulnerability to sleep-loss induced neurobehavioral impairments.

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Conflict of interest

The authors declare no competing financial interests.

4.2 Insufficient sleep: Enhanced risk-seeking relates to low local sleep intensity.

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Contribution: Experiment design, establishment of methods, data acquisition (including lead in experiment realization), data analysis and writing of the manuscript.

Abstract

Objectives: Chronic sleep restriction is highly prevalent in modern society and is in its clinical form, insufficient sleep syndrome, one of the most prevalent diagnoses in clinical sleep laboratories, with substantial negative impact on health and community burden. It reflects every-day sleep loss better than acute sleep deprivation, but its effects and particularly the underlying mechanisms remain largely unknown for a variety of critical cognitive domains, as for example risky decision-making.

Methods: We assessed financial risk-taking behavior after 7 consecutive nights of sleep restriction and after one night of acute sleep deprivation compared to a regular sleep condition in a within-subject design. We further investigated potential underlying mechanisms of sleep loss induced changes in behavior by high-density electroencephalography recordings during restricted sleep.

Results: We show that chronic sleep restriction increases risk-seeking, while this was not observed after acute sleep deprivation. This increase was subjectively not noticed and was related to locally lower values of slow wave energy during preceding sleep, an electrophysiological marker of sleep intensity and restoration, in electrodes over the right prefrontal cortex.

Interpretation: This study provides for the first time evidence that insufficient sleep restoration over circumscribed cortical areas leads to aberrant behavior. In chronically sleep restricted subjects, insufficient sleep over the right prefrontal cortex - which has been shown to be linked to risk behavior – leads to increased and subjectively unnoticed risk-seeking.

Introduction

The insufficient sleep syndrome is a very prevalent sleep-wake disorder which negatively impacts health and causes major community burden (Hillman & Lack, 2013; Pallesen et al., 2011). In affected subjects, excessive daytime sleepiness is caused by behavior, i.e. chronic sleep restriction (SR), and not by a medical pathophysiology (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). Accordingly, the current diagnostic criteria require that a patient's sleep time is usually shorter than expected for age (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). Chronic SR generally affects large parts of modern society (Basner et al., 2013; Groeger et al., 2004; Liu et al., 2016; Tinguely et al., 2014; Watson et al., 2015b). Apart from sleepiness, regular sleep durations of less than 7 hours per night causes impairments in cognitive performance involving vigilant attention, cognitive processing speed, and working memory (Watson et al., 2015b).

However, the majority of experimental studies on the behavioral effects of sleep loss focused on the effects of acute sleep deprivation (SD; Basner et al., 2013), a term used to indicate the full absence of sleep for an entire night or a longer consecutive period of time. In contrast to chronic SR, however, acute SD does not reflect a major socio-medical problem. It is currently unclear whether effects observed after SD also apply to chronic SR (Basner et al., 2013; Drummond et al., 2012; Van Dongen, Maislin, et al., 2003). As a consequence, the effects and underlying mechanisms of chronic SR, despite reflecting every-day sleep loss much better than acute SD, remain largely unknown for a variety of critical cognitive domains.

Decision-making in chronically sleep-restricted people has hardly been studied so far but is crucial for activities of daily living and particularly essential for economic and political leaders (Harrison & Horne, 2000; Thórisdóttir & Karólínudóttir, 2014). Over 40% of managers of companies and enterprises sleep 6 hours or less per night (Luckhaupt et al., 2010). These figures clearly indicate that we need insights into the effects of insufficient sleep on decision-making, including financial risk-taking. Some studies investigated risk-taking after acute sleep deprivation. The results on the influence on risk-taking have been mixed though (Acheson, Richards, & de Wit, 2007; Killgore, Grugle, & Balkin, 2012; Killgore, Kamimori, & Balkin, 2011; McKenna, Dickinson, Orff, & Drummond, 2007; Menz, Büchel, & Peters, 2012; Mullette-Gillman, Kurnianingsih, & Liu, 2015; Venkatraman, Chuah, Huettel, & Chee, 2007; Venkatraman, Huettel, Chuah, Payne, & Chee, 2011), probably due to different paradigms and protocols. However, up to date no paper assessed physiological brain measures related to risk-taking after SR.

Therefore, the aim of our study was to assess the effects of both chronic SR and acute SD on risk-taking, i.e., on individual risk-preferences, and to investigate underlying mechanisms of potential

changes after SR. Slow oscillating brain activity, namely slow waves during non-rapid eye movement (NREM) sleep are thought to reflect sleep intensity and the restorative function of sleep (Tononi & Cirelli, 2006). Slow waves are not equally distributed over the cortex but show local differences that vary between individuals (Finelli, Achermann, et al., 2001) and that can be assessed using high-density EEG (Lustenberger & Huber, 2012). Given that cognitive domains known to be impaired after sleep loss are processed in specific cortical areas, we hypothesized that local differences in sleep intensity during the short nights of SR would relate to eventual changes in risk-taking after SR. Recording EEG during task execution further allows the investigation of event-related potentials (ERPs) which reflect the neural underpinnings of changes in behavior (Polich, 2007). For instance, the stimulus-evoked P3 component amplitude, which is thought to reflect stimulus evaluation (Polich, 2007), has been found to be smaller when choices are consistent with a subject's preference for risk (Martin & Potts, 2009). Thus, we further hypothesized that eventually changed risk-taking behavior after sleep loss would also be reflected by altered P3 components during the actual choice process.

Methods

Experimental Design

We evaluated risk-taking in a controlled cross-over and within-subject protocol that included SR (7 nights during which time in bed was restricted to 5 hours per night) and SD (40 hours of continuous wakefulness), compared to a regular sleep condition (RegS) in a counterbalanced design (Fig 1). Risk-taking was assessed twice a day (afternoon and evening - to mitigate potential diurnal fluctuations of behavior) after RegS, after SR and after SD. Both SR and SD were preceded by one week of regular sleep-wake rhythm at home (eight hours in bed per night adapted to each subject's habitual bedtime). The interval between SR and SD was at least two weeks. SD was performed in the sleep laboratory under constant supervision. The first 4 nights and days of the SR protocol were performed at home, the last 3 nights in the sleep laboratory, which was achieved by delaying the bedtime by two hours and advancing the time of getting up by one hour. Compliance outside the laboratory was ensured by wrist actigraphy (on the non-dominant wrist; light sensor data included, ActiWatch, Neurotechnology; Morgenthaler et al., 2007), sleep diaries, and phone calls. Daytime napping was not allowed throughout the protocol. Furthermore, subjects were asked to abstain from caffeine, alcohol, and medication intake, starting 3 days prior to SR and SD and lasting throughout the protocol. Smokers were further requested not to increase their habitual cigarette consumption, and to not smoke at least 30 minutes prior to each assessment. This 30-minute restriction also applied to food intake.

A control group, to evaluate repetitive test effects, (consisting of another group of male subjects) maintained a regular sleep-wake rhythm with eight hours in bed per night for two weeks in total, controlled by wrist actigraphy and sleep diaries. Behavioral assessments in this group took place during the second week at the same times as during RegS followed by SR in the experimental group (cf. Fig 1B). All study-related restrictions were identical to the experimental group.

Participants

Fourteen healthy, right-handed, male participants, aged between 18 and 28 years (21.9 ± 3.0, mean ± s.d.) were recruited from a student population. Female subjects were not included in this study to avoid confounds by different time points of the menstrual cycle (Driver & Baker, 1998; Fernández et al., 2003; Wright Jr & Badia, 1999) which would have been unavoidable due to the lengthy study protocol. Subjects were carefully screened for exclusion criteria that may potentially affect brain functioning, sleep physiology, or risk-taking. These encompassed clinically relevant diseases, regular medication intake, history of a seizure or moderate to severe traumatic brain injury, history of sleep-wake disorders or complaints (including excessive daytime sleepiness and irregular sleep-wake rhythm), drug or alcohol abuse, long (>9 hours per night) or short sleepers (<7 hours per night), recent travelling across more than two time zones, more than five drinks or food items containing caffeine per day, more than ten cigarettes per day, and subjects studying mathematics, physics, computer science, economics, or psychology as these students might be familiar with behavioral test settings or their analyses. A screening night was further performed to exclude any undiagnosed sleep disorders, to assess sleep efficiency, and to let the subjects adapt to the lab environment. In general, the same procedure applied to the control group (n = 14, aged between 18 and 29 years; 22.5 ± 3.1), but no sleep EEG was recorded in the inclusion procedure. All subjects received fixed and variable (depending on task outcomes) monetary compensation for study participation. The local ethics committee approved the study (cantonal ethics commission Zurich, KEK-ZH-Nr. 2012-0496; registration at clinicaltrials.gov: NCT02305225) and written informed consent was obtained from all participants.

Assessment of Risk-Taking

To determine individual risk-preferences we used a binary probabilistic decision task adapted from Levy, Snell, Nelson, Rustichini, and Glimcher (2010). On every trial, subjects had to choose between a specified amount of money paid out with a certain probability (requiring risk-taking) or a lower amount of money paid out for sure (Fig 1). Both options were displayed simultaneously

on either side of the computer screen (spatial position of options was randomized across trials). We used four different levels of probability in the risky options (20%, 40%, 60% and 80%) and all of these risky offers were matched with a certain monetary amount to keep the expected value (EV = p * v, with p = probability, v = value) fixed at 20 Swiss Francs (100, 50, 33.30 and 25 Swiss Francs, respectively). Each probabilistic offer was paired with 22 linearly increasing certain choice alternatives ranging from 1.75 to 38.30 Swiss Francs. These ranges were optimized in a pilot experiment to capture the risk attitudes of our participant population. All pairs of options were repeated four times per session in a random order, adding to a total of 352 trials. Maximal time given to indicate the choice by left or right key press was 8 seconds, therefore ensuring spontaneous, realistic answers, but giving enough time to process the displayed information. The next trial appeared 1 second after the preceding choice, or after 8 seconds if no answer had been given (mean ± s.e.m number of trials without response was 0.0 ± 0.0 after RegS, 0.3 ± 0.2 after SR and 3.2 ± 1.7 after SD). During the task, the subject was monitored by video surveillance. After each session, subjects were asked to rate how often they thought to have chosen the risky option using a visual analogue scale, ranging from “never risky” to “always risky”. One subject was excluded from the analysis of subjective risk-taking due to missing data in one condition. To ensure that decisions were taken in an incentive-compatible fashion, we randomly selected one trial at the end of some sessions (determined by coin flip) and played out the trial according to the subject’s decision (for risky options a lottery with the given probability was played by open dice toss).

The total risk premium was calculated for each session as the main outcome measure of a subject’s risk-preference. It indicates by how many percent a subject undervalues a risky option compared to its objective expected value (EV). The risk premium of a specific probability was defined in % as (EV - CE) / EV * 100, where the certainty equivalent (CE) is the amount of money that a subject treated as equally desirable as the risky option. We calculated the CE by sorting trials of each probability level according to their certain amount (ascending) and determining the choice reversal point at which subjects switched from the probabilistic option to the certain alternative. If a subject’s behavior is risk-neutral then CE equals EV, resulting in a risk premium of 0%. Risk aversion is expressed as a positive value, reflected by a smaller CE than EV. Conversely, risk-seeking is expressed as a negative value, reflected by a larger CE than EV. We assessed the consistency of observed choices with the inferred risk-preference by counting how often the subject’s choices were inconsistent with the estimated CE. The number of deviations (x) was transformed by $\sqrt{x} + \sqrt{(x+1)}$ to approximate a normal distribution of the data (analogue to the transformed frequency of lapses in vigilance – see below). To evaluate potential repetition effects, we administered the risk task repeatedly to a control group at the same time points as during SR in

the experimental group (6 repetitions in total over the course of 8 days, cf. Fig 1B). We excluded two subjects from the control group, one due to acute illness and one due to missing the last assessment. We found that the risk premium was different from the following assessments up to the third repetition of the task and was stable afterwards in the control group (Helmert Contrasts following a significant effect in the repeated measures ANOVA: first to following: F (1, 11) = 23.40, P = 0.001, second to following: F (1, 11) = 9.56, P = 0.01, third to following: F (1, 11) = 10.73, P = 0.01, fourth to following: F (1, 11) = 0.28, P = 0.61.; fifth to sixth: F (1, 11) = 0.004, P = 0.95). As a result, we included two habituation test sessions in the experimental group before starting the first sleep manipulation (either before SR or SD, Fig 1B). Along the counter-balanced design, half of the subjects in the experimental group performed SR before RegS followed by SD and the other half performed first SD before RegS followed by SR (cf. Fig 1B).

Assessment of Vigilance and Sleepiness

To exclude that changes in risk-preferences are merely a result of impaired vigilance we also acquired the psychomotor vigilance test (PVT-192, Ambulatory Monitoring Inc.; Dinges & Powell, 1985), a sustained visual vigilance reaction-time task. We investigated the number of lapses which corresponds to trials for which the subject was not able to respond within 500 ms. The number of lapses (x) was transformed by $\sqrt{x} + \sqrt{(x+1)}$ to approximate normal distribution of the data (Dinges et al., 1997). In addition, we assessed subjective excessive daytime sleepiness before and after the seven nights of SR with the Epworth sleepiness scale.

Assessment of Sleep

Sleep was recorded in the sleep laboratory at the Department of Neurology, University Hospital Zurich, using a high-density EEG net (Electrical Geodesics Inc. Sensor Net for long-term monitoring) consisting of 128 electrodes. Impedances of all electrodes were kept below 50 kΩ, and data was recorded with a sampling rate of 500 Hz. Offline data processing, including filtering (0.5 Hz high-pass, 40 Hz low-pass filter), artefact and bad quality channel rejection, sleep stage scoring, re-referencing of data to the average of all electrodes, spectral analysis and interpolation of previously excluded channels was conducted in MATLAB as reported previously (e.g., Wilhelm et al., 2014). We quantified the extent of slow waves during sleep by slow wave energy (SWE), i.e. the summed the whole-night mean spectral power in the range of 0.75 – 4.5 Hz of all artefact-free NREM 2 and NREM 3 epochs. As in previous studies assessing topographical differences (Finelli, Achermann, et al., 2001; Wilhelm et al., 2014), we normalized the obtained

power values resulting in individual topographical distributions indicating relative SWE values at every electrode (expressed as % of average SWE over all electrodes of a subject). Without the excluded channels below the ears (which were excluded from further analysis to avoid artefacts induced by facial and neck muscles), our topography finally consisted of 109 electrodes.

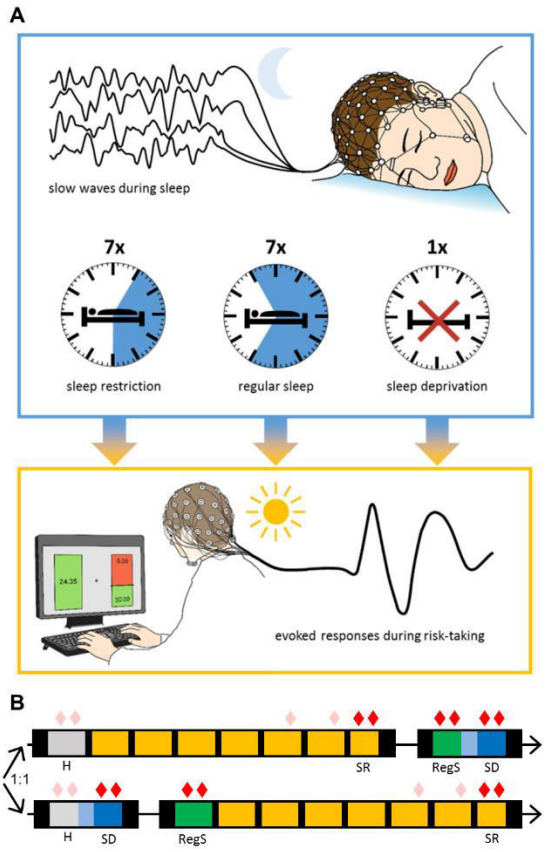

Figure 1 - Study Setup. (A) Schematic study design. Risk-taking behavior was assessed in the same subjects after 7 nights of regular sleep (8 hours in bed per night) and compared to behavior after 7 nights of sleep restriction (5 hours in bed per night), and after a night of sleep deprivation (one night without sleep). High-density EEG recordings were performed during sleep and during task execution. In the risk task subjects had to choose between two options represented by two bars (in this example left reflects the safe and right the risky option). Numbers in the bar: money value in Swiss Francs. Green bar height: probability level of receiving the money. Red bar height: probability level of getting nothing (0.00). When the right bar was chosen there was a 40% chance to win 50 Swiss Francs and a 60% chance of getting nothing, when the left green bar was chosen the chance was 100% to receive 24.35 Swiss Francs in this trial. (B) Detailed study design. Regular sleep (RegS, green), sleep restriction (SR, orange) and sleep deprivation (SD, blue) in a counterbalanced cross-over design (upper and lower line show the two possible sequences of conditions), with repeated behavioral tests (red and pink rectangles). Black bars: nights with 8h (broad bars) and 5h (thin bars) time in bed. H (gray): assessments performed to habituate a subject to the tests. Red rectangles: data points analyzed in this manuscript, including 2 assessments per day (approx. 2pm and 7.30pm) after the last night of SR, during SD and RegS. Pink rectangles: data points not included in the analysis.

Assessment of Event-Related Potentials

EEG during the risk task sessions was recorded using 64 channel EEG cap (EasyCap, Brain Products GmBH), with the reference at FCz and all electrode impedances kept below 5 kΩ. Data were sampled at 1000 Hz and processed offline using MATLAB applying standard routines.

Processing of the data included filtering (zero-phase butterworth IIR filter of fourth order; high-pass 0.8 Hz (having proofed the best compromise of enough suppression of the low-frequency shifts in the signal and fairly preserved amplitudes of the P3 component in our exploratory analysis), low-pass 30 Hz), visual removal of noisy sections and channels of poor quality, artefact removal by independent component analysis (ICA; extended runica function: Delorme & Makeig, 2004), stimulus-locked epoching (-200 to 1000 ms after stimulus onset), spherical interpolation of previously rejected channels (EEGLAB toolbox: Delorme & Makeig, 2004), re-referencing to the average signal across all electrodes, baseline-correction (200 ms to 50 ms before stimulus) and final visual trial rejection. For the analysis of the ERPs, only 8 out of the 14 subjects could be included. Four subjects were excluded due to strong sleep-loss induced alpha-activity (Cajochen, Brunner, Kräuchi, Graw, & Wirz-Justice, 1995) contaminating the ERP components (Woodman, 2010; which interfered with artefact identification in the ICA), one subject's RegS EEG data were not available due to technical failure, and one subject showed no identifiable ERP components.

We finally selected all processed ERP epochs corresponding to trials in which the risky option had been selected after stimulus presentation and response time was higher than 300 ms (on average 163.4 ± 11.8 (mean ± s.e.m.) after RegS and 177.9 ± 10.5 trials after SR). To assess the amplitude of the P3 component, we averaged the amplitude of the ERP over a time window from 250 to 400 ms after the stimulus (Polich & Kok, 1995) in every electrode.

Statistical Analysis

We performed a mixed analysis of variance (ANOVA) for the RP and subjective risk-taking measures after testing for normal distribution (Shapiro-Wilk test) with within-subject factors condition (RegS, SR, SD) and daily time point (1, 2) and the between-subject factor order (SD-RegS-SR, SR-RegS-SD). In case of a significant main or interaction effect, we performed a-priori defined simple contrasts, comparing the SR and SD conditions to RegS.

For the consistency of choices in the risk-task and the lapses in the PVT, we performed a repeated-measure Friedman's ANOVA with all six assessments (both time points at RegS, SR and

SD) as factor levels since the variables were not normally distributed in at least one condition even after transformation. To stay consistent with the parametric procedure, we performed a-priori defined post-hoc comparisons according to the contrasts in the parametric procedure with the Wilcoxon Signed Ranks Test. Having only one factor did not allow us to restrict the number of post-hoc comparisons in case of a significant result in Friedman's ANOVA. Hence, in this case we controlled for multiple testing by applying Bonferroni correction to P-values (multiplying the P-values by 5, corresponding to the number of performed post-hoc comparisons). To test for any order effects, we performed a post-hoc between-group comparison on the above mentioned differences using the Mann-Whitney *U*-test with the same Bonferroni correction.

Frequencies were compared using Pearson's chi-square test and relationships between measures were assessed by Pearson's correlation coefficients, which were tested for significance by permutation testing (5000 permutations of the subject order in the data) whenever one variable were not normally distributed. Electrodes were only considered significant when forming a cluster of at least 5 neighboring electrodes for SWE data (as with 109 electrodes tested and an alpha level of 0.05 this number corresponds to the number of expected false-positives) or 3 neighboring electrodes for ERP data, respectively. By restricting the possible location of the electrodes, the actual probability of false-positives is much lower.

All statistical analyses were performed using SPSS (IBM SPSS Statistics) or MATLAB.

Results

Effects of SR and SD on Risk-Preference

The mixed analysis of variance (ANOVA) for the risk-preferences RP% revealed a significant effect for the factor sleep condition only (F (2, 24) = 3.72, P = 0.04, all other factors and interactions: P > 0.24). Planned contrasts comparing risk-preferences both after 7 nights of SR and after SD to RegS revealed that only SR resulted in increased risk-seeking (Fig 2A; mean risk premium ± s.e.m after RegS: 7.8 ± 5.2%, after SR: -2.3 ± 6.4%, after SD: 7.6 ± 5.5%,). Most subjects were risk-aversive after RegS, which is in agreement with the well-documented risk-avoidance for gains (Fig 2B; $\chi 2$ (1) = 4.57, P = 0.03; Kahneman & Tversky, 1979). This was no longer observed after SR ($\chi 2$ (1) = 0.29, P = 0.59). Compared to RegS, the clear majority of subjects, i.e. 11 out of 14 showed an increase in risk-seeking after SR (Fig 2B; $\chi 2$ (1) = 4.57, P = 0.03), and 6 of them changed from being risk-aversive after RegS to being risk-seeking after SR (red dots in Fig 2B; risk premium in those subjects after RegS: 6.3 ± 3.3%, after SR: -12.3 ± 6.2%). That is, subjects moved towards a more risk-seeking attitude after SR. The extent of

increase in risk-seeking after SR was independent of the individual baseline level of risk-preference after RegS (r (12) = 0.04, P = 0.90, two-sided). This means that both risk-averse and risk-seeking subjects increased their preference for risk after SR. Furthermore, individual preferences after SR were not closer to risk-neutrality (i.e., zero) than after RegS (absolute difference to risk-neutrality after RegS: 14.4 ± 4.0%, after SR: 17.5 ± 4.2%; t (13) = -0.82, P = 0.43, two-sided paired-samples t-test). Hence, SR does not lead to risk-neutral behavior but rather to a significant increase in risk-seeking. Assessing the subjective ratings of risk-taking behavior revealed that participants were not aware of their increased risk-seeking after SR, as the mixed ANOVA showed no significant effect for either factor (all P > 0.26, Fig 2C; values after RegS: 60.0 ± 5.3%, after SR: 60.0 ± 3.7%, after SD: 58.5 ± 4.2%). Hence, altered risk-taking behavior did not reflect a conscious intentional reaction to the SR and was not even perceived by the subjects.

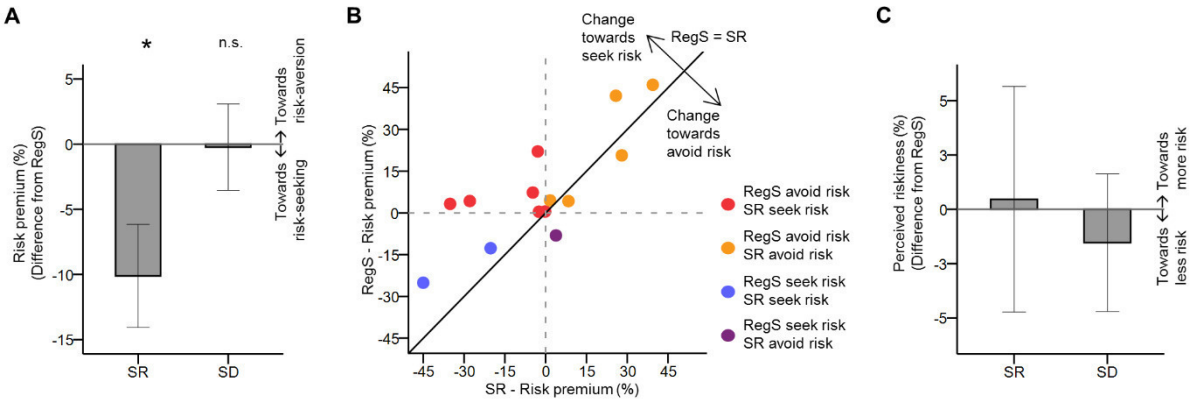

Figure 2 - Changes in risk-taking behavior following sleep restriction (SR) and (SD) compared to regular sleep (RegS). (A) Changes in risk-preferences. *F (1, 12) = 6.04, P = 0.03; n.s.: F (1, 12) = 0.01, P = 0.94 (two-sided)). (B) Difference plot of risk premium values after RegS and after SR. Deviation from the diagonal indicates the amount and direction of change in each subject. (C) Changes in subjectively reported percentage of risky choices. No planned contrasts performed. Zero represents no change compared to RegS, bars indicate means ± s.e.m.

Effects of SR and SD on Vigilance and Consistency of Choices

After chronic SR, subjective excessive daytime sleepiness as assessed with the Epworth sleepiness scale increased markedly compared to pre-SR conditions (median [interquartile range] pre-SR: 5.5 [3.8, 7.3], after SR: 10.5 [6.8, 13.5], z = -3.1, P = 0.002, two-sided). The increase in excessive daytime sleepiness did not correlate with changes in risk-taking behaviour after chronic SR (r (12) = -0.42, P = 0.13, two-sided, permutation testing).

Following a significant result in Friedman's ANOVA for the number of lapses in the PVT ($\chi 2$ (5) = 35.94, P = 0.000), planned post-hoc comparisons revealed that sustained attention was only significantly impaired after SD but not after SR (Fig 3A; median [interquartile range] number of transformed lapses after RegS: 2.0 [1.0, 2.5], after SR: 2.1 [1.5, 5.2], after SD: 4.5 [2.8, 7.4]; all comparisons for time points, interaction and order: P > 0.49). The impairment in vigilance was further not associated with changes in risk-preferences after SR or SD (SR: *r* (12) = 0.19, P = 0.51; SD: *r* (12) = -0.04, P = 0.87, both P-values: two-sided, permutation testing). Parallel to vigilance, we evaluated how consistent the choices in the risk task were with the inferred risk-preference (i.e., how stable the estimated risk-preferences were expressed across trials for each subject). Following a significant result in Friedman's ANOVA ($\chi 2$ (5) = 24.50, P = 0.000), post-hoc comparisons revealed that choice consistency was significantly reduced only after SD but not SR (Fig 3B; transformed number of deviations after RegS: 10.2 [8.2, 11.6], after SR: 10.9 [10.1, 12.0], after SD: 12.4 [10.0, 15.3]; all comparisons for time points, interaction and order: P > 0.07). Furthermore, changes in consistency were not associated with changes in risk-preferences (SR: *r* (12) = -0.24, P = 0.41; SD: *r* (12) = -0.31, P = 0.26, both P-values: two-sided, permutation testing). This again indicates that SR merely affected risk-preferences but not general behavioral variability that may reflect attentional lapses.

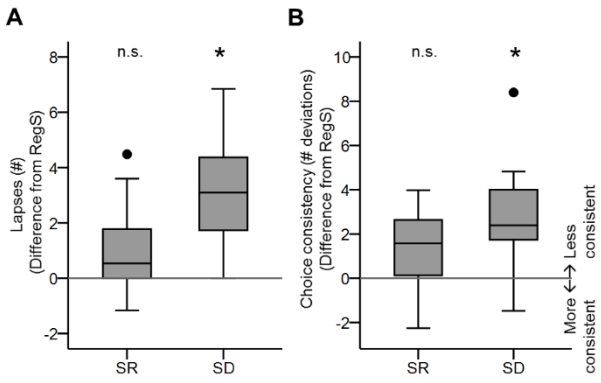

Figure 3 - Changes in vigilance and choice consistency following sleep restriction (SR) and sleep deprivation (SD) compared to regular sleep (RegS). (A) Vigilance, i.e. transformed number of lapses in the psychomotor vigilance test (PVT). (B) Consistency of choices over all trials, i.e., transformed number of trials in which the choice deviated from the inferred risk-preference. Box plots indicate medians (horizontal line), upper and lower quartiles (box), and extrema (whiskers); outliers are shown as black dots. *P < 0.05 (lapses RegS vs. SD: z = -3.18, P = 0.01; Choice consistency RegS vs. SD: z = -2.92, P = 0.02), n.s.: P > 0.05 (lapses: RegS vs. SR: z = -1.87, P = 0.31; Choice Consistency: RegS vs. SR: z = -2.10, P = 0.18), P-values: two-sided testing with post-hoc Bonferroni correction.

Association of Changes in Behavior with the Restorative Function of Sleep

To examine whether the observed significant shift towards risk-seeking was associated with differences in local sleep intensity we correlated all-night SWE during the last night of SR with the increase in risk-seeking after SR (risk premium (%) after RegS minus risk premium (%) after SR) Production of less SWE in a right prefrontal cluster of 6 electrodes was indeed linked to increased risk-seeking the following day (Fig 4B). Low levels of right prefrontal SWE were highly specific for predicting an increase in risk-seeking after SR (Fig 4C).

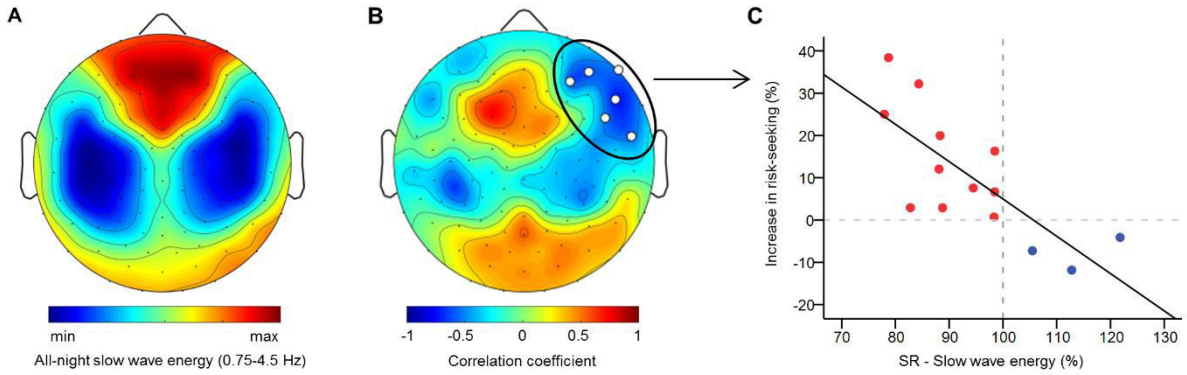

Figure 4 - Slow wave energy (SWE) topography and the correlation of SWE with the increase in risk-seeking after sleep restriction (SR) relative to regular sleep (RegS). (A) Whole-night SWE topography (average of all subjects) during the last night of SR. SWE values at every electrode were normalized in relation to average SWE over all electrodes of a subject. Dark blue to dark red colors indicate minimal (42%) to maximal (170%) SWE. (B) Topographical distribution of Pearson's correlation coefficients between normalized SWE during the last night of SR and the increase in risk-seeking after SR. White dots: significant cluster of electrodes (all $P < 0.05$, permutation testing, two-sided). (C) Relationship between averaged SWE in the cluster and the increase in risk-seeking after SR ($r(12) = -0.76$, $P = 0.001$, Pearson's correlation coefficient, permutation testing, two-sided). Dotted lines: no change in risk-seeking or average SWE (relative to the other electrodes of a subject). Red: subjects with increased risk-seeking and below average SWE. Blue: subjects without increased risk-seeking and above average SWE.

Association of Changes in Behavior with Stimulus-Evoked Potentials

To further corroborate that changed local electrophysiological processes contribute to altered risk-seeking behavior, we investigated whether increased risk-seeking after SR is also reflected by altered P3 components during the actual choice process. As anticipated, increased risk-seeking after SR was reflected by reduced P3 components over the right prefrontal cortex (rPFC) during presentation of the choice options for risky decisions (Fig 5).

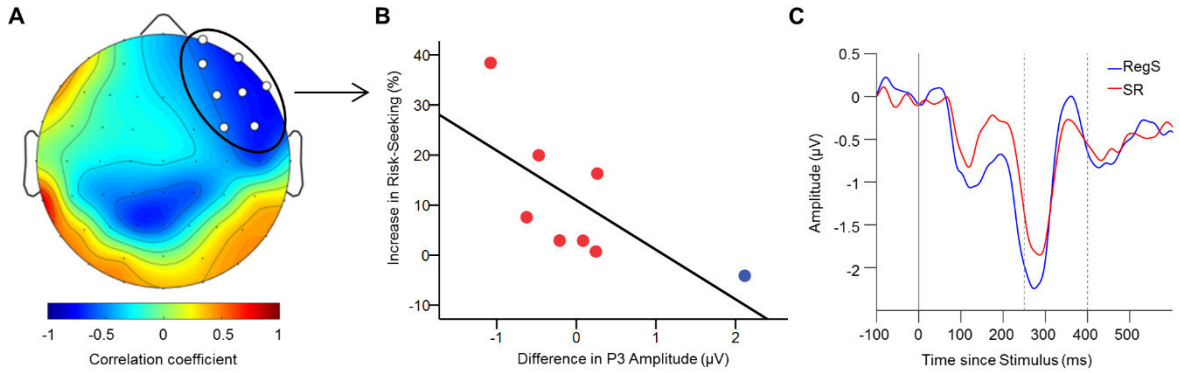

Figure 5 - Correlation between the difference in stimulus-evoked P3 amplitude preceding risky choices and the increase in risk-seeking after sleep restriction (SR). (A) Topographical distribution of Pearson's correlation coefficients. White dots: significant cluster of electrodes (all $P < 0.05$, permutation testing, two-sided). (B) Relationship between the average difference in amplitude in the cluster and the increase in risk-seeking after SR ($r(6) = -0.69$, $P = 0.01$, Pearson's correlation coefficient, permutation testing, two-sided). Red: subjects with increased risk-seeking. Blue: subject without increase. (C) Grand-mean over all averaged electrodes in the significant cluster over all subjects during the regular sleep (RegS) condition and SR. Zero: stimulus onset. Dotted lines: time window in which the amplitude was averaged to assess P3 amplitude.

Discussion

This study provides first-time evidence that chronic SR as it occurs in the prevalent insufficient sleep syndrome negatively affects decision-making behavior in association with locally decreased sleep restoration over circumscribed cortical areas. In chronically sleep restricted subjects, insufficient sleep over the right prefrontal cortex - which has been shown to be linked to risk behavior – leads to increased and subjectively unnoticed financial risk-seeking - without major effects on vigilance or the consistency of choices with the subject's risk-preference. On the other hand, SD did not affect a subject's preference for risk but lead to reduced choice consistency coupled with impaired vigilance. While these latter effects of SD are in line with previous results (Menz et al., 2012; Mullette-Gillman et al., 2015; Venkatraman et al., 2007) and may mostly reflect behavioral instability, the divergent findings imply that not all aspects of acute SD can be generalized to other forms of sleep loss such as chronic SR. The increase in risk-seeking after SR was subjectively not noticed, indicating a misperception of altered decision-making, which fits the previously reported underestimation of cognitive impairments after SR (Van Dongen, Maislin, et al., 2003). Up to date, only one study investigated impulsive-risk taking after mild chronic sleep restriction (Demos et al., 2016), but found no effects on risk-taking, yet on impulsive action. However, it has been shown before that sleep deprivation leads to increased effort discounting (Libedinsky et al., 2013), which can mask effects on risk-preferences when no forced choice

paradigm is used, as it is the case in the task applied in that study, i.e., in the balloon analogue risk task (BART; Lejuez et al., 2002). Furthermore, the study did not include any physiological brain measures - including sleep parameters *per se* – which made it impossible to investigate by what mechanisms chronic sleep loss might have altered decision-making. Considering that the cause for the insufficient sleep syndrome, i.e. chronic SR is a highly prevalent condition in modern societies, with 30% or more of the population in various countries reporting inadequate sleep durations (Groeger et al., 2004; Liu et al., 2016; Tinguely et al., 2014), our findings further emphasize the importance of investigating the effects of chronic SR.

We found that lower SWE over the rPFC during SR relate systematically to the increase in risk-seeking after SR. Hypo-activity of the rPFC during rest is a dispositional indicator of risk-seeking (Gianotti et al., 2009). Hence, insufficient restoration during chronic SR might have an impact on rPFC function, resulting in effects similar to those of experimental rPFC disruption (Knoch et al., 2006). This conjecture is further supported by the finding that the increase in risk-seeking after SR is related to a reduction of rPFC responsiveness during the processing of the choice options for the risky decision. While it has been shown before that consequent increases in slow waves are linked to plastic processes occurring during learning (Huber et al., 2004), we show here that the local extent of slow waves during restricted sleep periods is linked to sleep-loss induced changes in behavior. To the best of our knowledge, such a direct link between local electrophysiological correlates of the restorative function of sleep and changes in behavior resulting from insufficient sleep has not been shown before.

Slow waves result from synchronous activity of neuronal populations (Esser, Hill, & Tononi, 2007; Vyazovskiy et al., 2009). The intensity of slow waves varies due to differences in strengths of connections or relative regional density (Tononi & Cirelli, 2006). The topography of slow waves is highly stable within an individual and thus is thought to reflect individual traits of functional anatomy (Finelli, Achermann, et al., 2001). Hence, SWE might not only indicate how much restoration is obtained during the night but could also reflect stable degrees of a brain structure's functional integrity, with higher levels of integrity making a structure more robust against function deterioration when challenged by SR. Future studies manipulating slow waves in the rPFC could help to determine whether functional deterioration after sleep loss is determined by the extent of sleep-related restoration or by more stable neuro-anatomical differences.

Our results imply that the insufficient sleep syndrome might come along with further, until now unrecognized alterations of behavior, beside the defining and up-to now identified secondary symptoms, like for example dysphoria or reduced motivation (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014), with potentially negative

consequences. The observation that chronic SR can cause aberrant behaviour even independent of a subjective feeling of sleepiness further indicates that the current definition of insufficient sleep syndrome might be too narrow (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). A further increase in risk-seeking due to insufficient sleep might be particularly problematic in individuals who already have a high preference for risk *per se*. While over 70% of business students report to obtain subjectively insufficient or highly insufficient sleep (Tsui & Wing, 2009), they are also more risk-seeking than the general public (Sjöberg & Engelberg, 2009) and the economic crisis in 2008 is at least partly attributed to risky business decisions (Thórisdóttir & Karólínudóttir, 2014). Nevertheless, the prevalence of short sleep durations due to extended working hours and commute time is increasing in modern society (Basner et al., 2007; Basner et al., 2013; Tinguely et al., 2014). An alarming additional result is our observation that sleep-restricted subjects do not notice their increased drive for risk-taking. While we cannot exclude that individuals in positions that require high-impact decision-making may be more resilient to the effects of sleep restriction, our results suggest that all of us, but particularly leaders of companies and countries, are well advised to work and make decisions only when fully sleep-satiated.

Acknowledgments

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Author contributions

C.R.B., R.P. and R.H. contributed equally to study design and direction. A.M., J.L., E.M., and M.S. performed the sleep-laboratory based experiment supervised by R.P. and E.W. S.W. J.L. and A.M. analyzed the risk task data supervised by C.C.R. A.M. analyzed the sleep data supervised by R.P., E.W. and R.H. E.M. and A.M. analyzed the ERP data supervised by R.P. and R.H. M.S. and

A.M. analyzed the PVT data supervised by E.W. A.M. drafted and C.R.B., R.H., R.P., E.W., C.C.R., and S.W. edited the manuscript. All authors approved the final version of the manuscript.

4.3 The impact of sleep restriction and sleep deprivation on subjectively perceived and actigraphically derived sleep parameters.

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*these authors contributed equally to the study.

Contribution: Experiment design, establishment of methods, data acquisition (including lead in experiment realization), data analysis and co-writing of the manuscript.

Submitted version (un-refereed author version).

Abstract

Objectives

To investigate the effect of increased sleep pressure and shortened sleep duration on subjective sleep perception and actimetry sleep estimates in relation to electroencephalographic sleep measures.

Methods

Fourteen healthy male volunteers completed a baseline (BL) assessment with 8 hours time in bed, a sleep deprivation (SD, no sleep) and a sleep restriction (SR) protocol with 5 hours time in bed in seven consecutive nights. We assessed perception index (PI) and actimetry index (AI), derived through dividing the subjectively perceived or actimetry estimated total sleep time (TST), wake after sleep onset (WASO) and sleep latency (SL) duration by the objectively measured one in minutes at each time point: BL, last SR night and recovery night after SD.

Results

TST was subjectively underestimated at BL and overestimated during SR and after SD, while actimetry underestimated TST at all timepoints, even more during SR and after SD. WASO was subjectively underestimated at all time points, even more during SR and after SD and actimetry always overestimated WASO. SL on the other hand was always overestimated subjectively and underestimated by actimetry. Subjective estimates regarding TST were closer to electroencephalography derived measures during SR and after SD and regarding WASO at all time points.

Conclusion

Self-assessments and actimetry data of patients with chronic SR should be interpreted with caution. The subjectively decreased perception of WASO could lead to an overestimation of sleep-efficiency in chronically sleep restricted individuals, while the underestimation of TST and overestimation of WASO by actimetry could lead to a further underestimation of the already low TST.

Keywords

insufficient sleep syndrome, sleep restriction, sleep deprivation, sleep duration, sleep perception, actimetry.

Introduction

Modern lifestyle with extended working hours and commute time, psychological stress, personal choices, social and family demands lead to increasing chronic sleep restriction (SR; Basner et al., 2007). A number of surveys in different countries have shown a decrease in subjectively reported sleep duration (Kronholm et al., 2008; "National Health Interview Survey. QuickStats: Percentage of Adults Who Reported an Average of <6 Hours of Sleep per 24-Hour Period, by Sex and Age Group - United States, 1985 and 2004.," 2005; Tinguely et al., 2014).

Acute sleep deprivation (SD) refers to no sleep or a marked reduction in total sleep time (TST), lasting one or two days, while chronic SR arises when the individual routinely sleeps less than required for optimal functioning. In studies, chronic SR is induced by limiting the number of hours in bed for several days. Chronic SR is far less examined than acute SD, probably due to demanding study protocols, even though it resembles sleep loss in everyday life much closer. Most studies focus on day-time consequences of SD and SR, mainly on impaired cognitive performance. Using the psychomotor vigilance task (Dinges & Kribbs, 1991) it was shown that behavioral alertness deteriorates progressively, when night-time sleep duration is limited to 3-7 hours for 7-14 nights (Belenky et al., 2003; Van Dongen, Maislin, et al., 2003).

According to the international classification of sleep disorders, 3rd edition, an insufficient sleep syndrome (ISS) occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014), which is a form of SR. Polysomnography is the gold standard for recording and quantifying sleep, yet it is time consuming, expensive and most often requires an inpatient setting. However, relying on subjective sleep estimates can be inconclusive since these measures do only correlate moderately with objective sleep parameters (Means et al., 2003) and patients suffering from ISS often do not realize that their sleep duration is insufficient (Komada et al., 2008). The exact factors influencing subjective sleep perception are still unclear. Self-rating of sleep, regarding sleep latency, duration and wakefulness after sleep onset (WASO) is rarely reported in SR protocols. A recent study which assessed sleep quality changes after partial sleep restriction found that during short nights subjective estimates and objective measures on average converged or were even inverted, but the authors did not investigate the change in discrepancy in further detail (Elmenhorst et al., 2008). However, the reported correlations were markedly weaker for the short nights compared to the normal nights. Hence, elevated sleep pressure and/or short sleep durations could themselves alter the accuracy of subjective sleep estimates.

Another technique to estimate sleep and wakefulness is activity monitoring by an accelerometer device (so called actimeter). Actimetry's role in sleep research is markedly increasing in recent years as a tool to monitor sleep-wake profile and sleep duration. It has been validated against the gold standard polysomnography in healthy volunteers and in patients with sleep disorders as insomnia and sleep disordered breathing (Dick et al., 2010; Lichstein et al., 2006; Marino et al., 2013; Sadeh, Sharkey, & Carskadon, 1994). Actimetry allows lengthy recordings during one up to 3-4 weeks and is more reliable than sleep logs (Ancoli-Israel et al., 2003). Even if it is not as precise as polysomnography in measuring sleep and wakefulness, it is particularly useful in monitoring treatment effects in circadian rhythm disorders and in some sleep disorders as insomnia, restless legs syndrome (Ancoli-Israel et al., 2003; Littner et al., 2003) and ISS (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). The method is regarded a useful and valid tool in measuring TST and WASO (Marino et al., 2013). It has also been applied in SR studies as the main tool estimating sleep quantity (e.g., Bei, Wiley, Allen, & Trinder, 2015; Lo, Ong, Leong, Gooley, & Chee, 2016). However, it remains unclear how elevated sleep pressure itself, as induced by SR for example, influences the accuracy of estimated sleep parameters.

We aimed at comparing objective sleep measures, acquired by sleep recordings to subjective sleep perception and actimetric sleep-wake assessment at baseline (BL), during the seventh consecutive night of SR and after a night of total SD. Thus we aimed at assessing whether increased sleep propensity as induced by SR and SD in combination with short bedtimes, as it is the case in SR, changes the accuracy of sleep perception in the same subjects and whether actigraphic or subjective measures better relate to objective measures in the condition of SR and SD.

Methods

Study design

The data used in this manuscript are part of a larger study with counterbalanced cross-over design, investigating different behavioral and electrophysiological aspects of acute SD (in total 40h) and chronic SR (seven nights with 5 instead of 8 h in bed per night). For the present work we analyzed sleep recordings, actimetry measurements and subjective self-assessment performed at baseline (BL), during the last (seventh) SR night, SR7 and after one night of total SD (=40 hours). The SR and SD protocols were separated by at least 2 weeks and were both preceded by one week of regular sleep-wake rhythm at home, controlled by actimetry and sleep logs. The SD protocol and the first 4 days and nights of the SR protocol were performed at home, and the last 3 evenings and

nights in the laboratory. The bedtimes in the protocol were adapted to each subject's habitual bedtime (± 1 hour). During SR bedtimes were delayed by two hours and wake-up times were advanced by one hour. Compliance, for the parts subjects performed at home, was ensured by wrist actimetry, sleep diaries, and also by phone calls. Daytime napping was not allowed throughout the protocol. Furthermore, subjects were asked to abstain from caffeine, alcohol, and medication intake, starting three days prior to SR and lasting throughout the protocol.

Participants

Fourteen healthy, right-handed, male participants were recruited from a student population (mean age 22.2 ± 3.1 (s.d.)). To ensure a homogenous study population, the subjects were carefully screened for exclusion criteria potentially having an influence on brain functioning or sleep physiology. These encompassed clinically relevant diseases, regular medication intake, sleep disorders or complaints, drug or alcohol abuse, long (more than nine hours per night) or short sleepers (less than seven hours per night), travelling across more than two time zones less than one month prior to the study. These criteria were reviewed by a telephone interview and questionnaires (including the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, the Fatigue Severity Scale, the Beck Depression Inventory and the Beck Anxiety Inventory). A screening night with polysomnography was further performed to exclude any undiagnosed sleep-wake disorders, to assess sleep efficiency, and to let the subjects adapt to the lab environment.

The local ethics committee approved the study and written informed consent was obtained from all participants.

Sleep recordings (sleep-EEG)

Sleep was recorded using a high-density electroencephalography (hd-EEG) net (Electrical Geodesics Sensor Net for long-term monitoring), consisting of 128 electrodes, including electrooculogram (EOG) and electromyogram (EMG). Sleep stage scoring was performed using frontal, central and occipital derivations (F3, F4, C3, C4, O1 and O2) against contralateral mastoids (M1 and M2) as well as EOG and EMG, according to standard criteria (Berry et al., 2012). Sleep latency (SL) was defined as the latency to the first epoch of stage NREM1 (N1).

Subjective sleep estimates

Within 30 minutes of waking-up after each sleep recording, participants filled in a short questionnaire, including subjective TST, subjective SL and subjective WASO.

Actimetry

Participants wore a wrist actiwatch (Actiwatch 2, Respironics, Inc.) on their non-dominant wrist during the one-week pre-study period to ensure regular sleep-wake profile and throughout the SR and SD protocols. Data were collected at 1 min resolution and were scored with the Actiware software (version 6.0.2, Respironics, Inc.). TST was calculated using a medium sensitivity algorithm, with which an acitivity count greater than or equal to 40 was defined as waking. Due to technical problems with the devices, data in two subjects had to be excluded. Additionally, one subject did not wear the actimeter at SR7.

Sleep perception/actimetry sleep estimation

Similar to Edinger and Fins (1995) and Goulart et al. (2014) sleep perception was measured using TST (in minutes) as perceived by the participants, excluding wake episodes at night divided by TST (from lights off to lights on) in minutes measured in sleep recordings. The result of this calculation yielded the so-called Perception Index (PI). A PI < 1 indicates an underestimation of TST by the volunteers, and a PI > 1 an overestimation. We also calculated the PI for sleep latency (using latency to N1 in sleep recordings) and WASO.

Similarly, we built an actimetry index (AI) between actimetry-estimated and polysomnographically measured TST, WASO and SL in order to evaluate which method closer resembles objective polysomnographic measures.

To avoid zero-values when calculating the PI and AI for WASO and SL, data were transformed according to the formula $\sqrt{x} + \sqrt{(x+1)}$ as previously reported (Dinges & Weaver, 2003).

Statistics

Shapiro-Wilk test of normality was performed for each variable. As PIs and AIs for TST were normally distributed we run a repeated measures (r) ANOVA with the factors time point (BL, SR7, SD) for both PIs and AIs to assess the change induced by SR and SD. If sphericity was

violated, Greenhouse-Geisser correction was applied. Following a significant effect in the rANOVA, we performed a-priori defined simple contrasts, comparing SR7 and SD to BL. For non-normally distributed data as PIs and AIs for WASO and SL we applied repeated measures Friedman's ANOVAs with the factor time point (BL, SR7 and SD) separately for PIs and AIs. Following a significant effect in Friedman's ANOVA, we conducted post-hoc comparisons for PIs and AIs of SR7 and SD to BL applying Wilcoxon signed rank tests with Bonferroni correction of the significance level (dividing the alpha-level of 0.05 by 2 for the two post-hoc comparisons). To assess whether PIs and AIs indicated a significant deviation from objectively observed measures, we tested all PIs and AIs against 1 (in normally distributed variables: one-sample t-test, in non-normally distributed: one-sample Wilcoxon signed rank test). In case there was no significant difference in the measures between BL, SR7 and SD, data was averaged across conditions for this comparison. If not, the significance level was again adjusted by Bonferroni correction (dividing by 3 for the three comparisons).

To assess whether AI or PI measures better reflect objective data at the different time points, we compared the absolute difference of corresponding AI and PI values to 1 (paired-samples t-tests for normally distributed data, Wilcoxon signed rank tests for non-normally distributed). In case there was no difference in AIs and PIs across BL, SR7 and SD, data was averaged across conditions for this comparison. If not, the significance level was again adjusted by Bonferroni correction (dividing by 3 for the three comparisons).

Results

Total sleep time

PIs showed a significant difference between BL, SR7 and SD in the rANOVA (F (1.163, 15.124) = 9.924, P = 0.005). Simple contrasts revealed that PIs at both SR7 and SD were significantly different to PIs at BL (SR7: F (1, 13) = 11.238, P = 0.005; SD: F (1, 13) = 9.204, P = 0.010). AIs on the other hand were not significantly different between BL, SR7 and SD according to the rANOVA (F (2, 20) = 1.128, P = 0.343).

Both PI and AI values for TST at BL were <1, showing an underestimation of sleep, whereas after SR and SD PIs increased, showing a marginal overestimation and AIs slightly decreased, showing a further underestimation (Figure 1a). In line with this, PI values at SR7 tended to be different from 1, while values at BL were significantly different from 1, but did not reach significance according to the applied Bonferroni correction (BL: t (13) = -2.239, P = 0.043; SR7: t (13) = 1.945, P = 0.074; SD: t (13) = 0.342, P = 0.738, significance level according to Bonferroni

correction: 0.017). AIs were significantly different from 1 averaged across all conditions (t (10) = -4.577, P = 0.001).

Comparing the distance to 1 between PIs and AIs we found that there was no difference in the distance to 1 at BL (t (10) = 0.492, P = 0.633). In contrast, the difference of AIs to 1 was significantly larger than the difference of PIs at SR7 and SD, but only the latter reached significance after Bonferroni correction (SR7: t (10) = -2.765, P = 0.020; SD: t (10) = -3.314, P = 0.008, significance level according to Bonferroni correction: 0.017). Hence, after sleep loss subjective estimates were closer to the TST determined by sleep EEG recordings than actigraphy derived estimates.

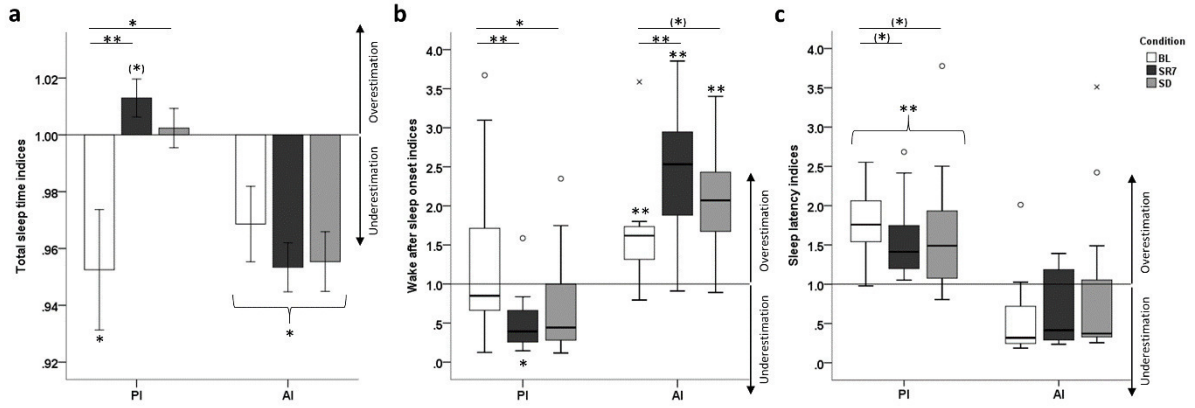

Figure 1 Perception indices (PI) and actimetry indices (AI) during baseline night (BL), the seventh night of sleep restriction (SR7) and recovery night after sleep deprivation (SD) for (a) total sleep time, (b) wake after sleep onset and (c) sleep latency . The PI and AI indicate how the sleep time estimates relate to sleep electroencephalography derived values (1 = identical). Bars represent means ± s.e.m., box plots indicate medians (horizontal line), upper and lower quartiles (box), and extrema (whiskers); outliers are shown as circles (1.5 - 3 times the interquartile range) and crosses (> 3 times the interquartile range). Stars represent on the one hand significant differences to 1 and on the other hand significant differences between timepoints. *p < 0.05, **p < 0.01, $^{(*)}$p > 0.1. Exact significances of the corresponding tests and Bonferroni adjusted levels of significance are given in the text.

Wake after sleep onset

Friedman's ANOVA showed a trend towards a difference in PIs for WASO between BL, SR7 and SD ($\chi 2$ (2) = 5.286, P = 0.071). Post-hoc tests revealed significantly lower PIs at both SR7 and SD (SR7: Z = -2.668, P = 0.008; SD: Z = -2.480, P=0.013; adjusted alpha-level according to Bonferroni correction: 0.025), with values at all time points < 1 showing a subjective

underestimation of WASO which is more pronounced at SR7 and SD (Figure 1b). When tested against 1, PI for WASO showed a significant underestimation of WASO only at SR7, whereas at BL and SD the values were not significantly different to 1 (BL: $Z = 0.282$, P = 0.778: SR7: $Z = -2.857$, P = 0.004; SD: $Z = -1.503$, P = 0.133; adjusted alpha-level according to Bonferroni correction: 0.017).

AIs for WASO were significantly different at different time points according to Friedman's ANOVA ($\chi 2$ (2) = 13.273, P = 0.001). AIs expressed an overestimation of WASO at all time points with values >1 and a further significant increase of this overestimation at SR7 and a trend after SD (Figure 1b; SR7: $Z = -2.934$, P = 0.003; SD: $Z = -1.867$, P = 0.062; adjusted alpha-level according to Bonferroni correction: 0.025). However, AI values were significantly higher than 1 at all time points (BL: $Z = 2.667$, P = 0.008; SR7: $Z = 2.845$, P = 0.004; SD: $Z = 2.845$, P = 0.004; adjusted alpha-level according to Bonferroni correction: 0.017).

Comparing the distance to 1 between PIs and AIs we found that there was no difference in the distance to 1 at BL ($Z = -0.445$, P = 0.657). In contrast, the difference of AIs to 1 was significantly larger than the difference of PIs at SR7 and SD, but only the former reached significance after Bonferroni correction (SR7: $Z = -2.490$, P = 0.013; SD: $Z = -2.223$, P = 0.026, significance level according to Bonferroni correction: 0.017). Hence, after sleep loss subjective estimates were closer to the WASO determined by sleep EEG recordings than actigraphy derived estimates.

Sleep latency

Friedman's ANOVA showed a trend towards a difference in PIs for SL at the different time points ($\chi 2$ (2) = 5.491, P = 0.064), and also post-hoc tests only showed a trend for lower PIs after SR7 and SD compared to BL (both: $Z = -1.664$, P = 0.096), with PIs at all time points showing a subjective overestimation (Figure 1c). This overestimation was significant for the averaged PIs across all time points with values being different to 1 (PI averaged at all time points: $Z = 3.296$, P = 0.001).

AIs for SL did not differ between time points according to Friedman's ANOVA ($\chi 2$ (2) = 3.455, P = 0.178). Even though actimetry underestimated SL at all time points with values <1 (Figure 1c), the difference to 1 averaged across all time points was not significant ($Z = -1.600$, P = 0.110).

As there were no significant differences between different time points for both PIs and AIs, we compared the absolute difference to 1 between PIs and AIs averaged across all time points and found no significant difference ($Z = -0.178$, P = 0.859). Hence, there was no difference between

subjective and actigraphy derived estimates in how close SL was to the SL derived by sleep EEG recordings.

Discussion

In the present study, we intra-individually examined the effects of chronic SR and acute SD on the assessment of TST, WASO and SL by subjective self-estimation and actimetry compared to sleep-EEG recordings. Subjective assessment and actimetry estimated TST differently and the assessment changed in opposite directions from BL to SR and SD with a shift in the subjective perception of TST with underestimation at BL and slight overestimation after SR and SD, whereas actimetry further underestimated TST after SR and SD. WASO was overestimated subjectively at BL and underestimated after SR and SD, while actimetry always overestimated WASO. SL was subjectively overestimated and underestimated by actimetry at all time points. Taken together, this implicates higher perceived sleep continuity after SR and SD. Interestingly, this increase in perceived sleep continuity even resulted in positive sleep misperception. This is in line with an epidemiological study which found that sleep duration is subjectively overestimated and that the extent of overestimation is more pronounced in shorter sleep durations (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008). However, this study judged the subjective estimation of sleep durations by comparing it to actimetry derived data. As we found that actimetry overestimated WASO in both sleep-satiated and sleep restricted condition and underestimated TST after SR and SD, this finding could also be a result of underestimated sleep durations by actimetry. Nevertheless, another study comparing patients with obstructive sleep apnea and patients with suspected, but afterwards unconfirmed sleep apnea found that the patients without apnea rather overestimated sleep durations while the confirmed sleep apnea patients showed an underestimation as has been previously seen in insomnia patients (Frankel et al., 1976; McCall et al., 1995) and also during sleep disruption by REM sleep deprivation (Goulart et al., 2014). As it is likely that one reason for suspected sleep apnea in the afterwards unconfirmed patients was the presence of excessive daytime sleepiness, one could hypothesize that increased sleep pressure leads to an overestimation of sleep times as seen in our study. Such a finding might not only be important to consider in the process of evaluating a potential ISS in patients, but could also partially explain why patients suffering from ISS are not aware how little sleep they actually get.

A potential underlying mechanism of the shift towards positive sleep misperception might be increased sleep pressure, as this results from both chronic SR and acute SD. Indeed, we found that subjective estimates always changed in the same direction after SR and SD. However, we also observed that subjective estimates of WASO only significantly differed from the sleep EEG

derived values during SR, but not after SD. Also TST only showed a statistical trend for overestimation during SR, but not after SD. Hence, it seems unlikely, that increased sleep pressure is the only mechanism leading to positive sleep misperception. This is in line with another study where no changes in TST estimates were found after SD (Goulart et al., 2014), although it is important to note that this was assessed in a between-subject design where a large inter-individual variability might have covered some effects. In contrast to recovery sleep after SD, time in bed was reduced during SR. Furthermore, SR is known to restrict both NREM and especially REM sleep (Banks et al., 2010). Hence, short sleep durations, increased REM sleep pressure or reductions in REM sleep are further potential underlying mechanisms of the induced positive misperception of sleep. However, increased REM sleep pressure does not seem likely to be responsible for the positive misperception, as an earlier study found no increase from baseline to undisturbed recovery nights after REM sleep deprivation (Goulart et al., 2014). While it is important to keep in mind that this study performed a between-subject comparison, their findings together with our results imply that the overestimation of sleep continuity found in our study is likely the result of shortened, but uninterrupted sleep, rather than resulting exclusively from increased sleep pressure or the reduction in REM sleep per se.

The perception of SL did not differ between sleep satiated and sleep loss conditions, yet the observed overestimation of sleep latency at all time points, as expressed through a sleep latency PI significantly larger than1 is in agreement with studies in patients with sleep disorders, where patients with insomnia, with sleep apnea, with excessive daytime sleepiness and also control subjects tended to overestimate their sleep latency (Chervin & Guilleminault, 1996; Lewis, 1969; McCall et al., 1995; Vanable, Aikens, Tadimeti, Caruana-Montaldo, & Mendelson, 2000). We must note that we used latency to N1 in sleep recordings and potentially deeper sleep, as N2 is needed for proper sleep perception. Yet, when we looked at the PIs for SL using N2 (data not shown), values were again >1.

Many SD and SR studies have reported controlling sleep with actimetry (e.g., Bei et al., 2015; Lo et al., 2016), yet none has compared sleep recordings to actimetry data in the condition of sleep loss and compared it to sleep satiated condition. When comparing actimetry to sleep recordings, we observed an actimetric underestimation of TST with values significantly below 1 and an overestimation of WASO at all time points with values significantly above 1. Actimetry validation studies state that actimetry usually underestimates WASO (Ancoli-Israel et al., 2003). Yet for mean WASO values close to 0, the actimetry device overestimates WASO (Marino et al., 2013), which is the most plausible explanation for our findings, as our subjects, being good sleepers had low WASO values already at BL. In this line the overestimation also increased after

sleep loss. However, as high sleep efficiency is expected in ISS, this finding might be of importance when evaluating patients potentially suffering from ISS. Another explanation is the actimetry setting. Validation studies report data collection resolution of 30 seconds, while in clinical studies (e.g., Bei et al., 2015; Lo et al., 2016), including ours, it is higher, (i.e., in our study one minute) which could have led to an overestimation of WASO. On the other hand, sensitivity in validation studies was set on high mode, whereas again in most clinical studies and in our one, it was set to medium, which would rather lead to an underestimation of WASO. As WASO and TST are dependent on each other, especially in a study with a preset time in bed, it is conceivable that overestimation of WASO would be accompanied by underestimation of TST by actimetry as a consequence. On the contrary, actimetry assessed sleep latency was similar to the one assessed with sleep recordings, using the first epoch of N1 as sleep onset. The main limitation of our study is the small number of participants, yet through the within-subject design we reduce data variability and manage to register a number of significant results. Another limitation is the inclusion of only male subjects, whose data might not apply to females. Indeed, it has been found that females show smaller differences between subjectively estimated and objectively measured sleep variables (McCall et al., 1995). When relating findings after SR to patients with ISS, we should note that our participants had shortened but regular bed times, whereas in insufficient sleep syndrome most often irregular rest/activity routine is observed.

In summary, we show that SR leads to a reversal in sleep perception, with sleep duration underestimation and WASO overestimation at BL and sleep duration overestimation and clear WASO underestimation during SR. Hence, a positive sleep misperception could explain why patients suffering from ISS are not aware of the full extent of sleep restriction they have. Sleep latency was subjectively overestimated in all conditions. This could prevent the recognition of increased sleep pressure or drive in these patients. In contrast, actigraphy overestimated WASO in all conditions and underestimated TST especially during SR and after SD. However, actigraphy proves to be a reliable measure of sleep latency. It is a useful method for controlling for regular bedtimes and time in bed, yet cannot be used for estimating sleep precisely. Thus, actimetry may underestimate the already low TST of patients with chronic SR and overestimate WASO, which could give the misleading impression of disturbed sleep. So in patients potentially suffering from ISS a possible subjective sleep duration and sleep latency overestimation and actimetry sleep duration underestimation and WASO overestimation should be taken in consideration when assessing patients' history and test results.

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4.4 Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial.

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Summary

Posttraumatic sleep-wake disturbances are common following acute traumatic brain injury. Increased sleep need per 24 h and excessive daytime sleepiness are among the most prevalent posttraumatic sleep disorders and impair quality of life of trauma patients. Nevertheless, the relation between traumatic brain injury and sleep outcome, but also the link between posttraumatic sleep problems and clinical measures in the acute phase after traumatic brain injury has so far not been addressed in a controlled and prospective approach.

We therefore performed a prospective controlled clinical study to examine (i) sleep-wake outcome after traumatic brain injury and (ii) to screen for clinical and laboratory predictors of poor sleep-wake outcome after acute traumatic brain injury. Forty-two out of 60 included patients with first-ever traumatic brain injury were available for follow-up examinations. Six months after trauma, the average sleep need per 24 h as assessed by actigraphy was markedly increased in patients as compared to controls (8.3 ± 1.1 h vs. 7.1 ± 0.8 h, $P < 0.0001$). Objective daytime sleepiness was found in 57% of trauma patients and 19% of healthy subjects, and the average sleep latency in patients was reduced to 8.7 ± 4.6 min (12.1 ± 4.7 min in controls, $P = 0.0009$). Patients but not controls markedly underestimated both excessive sleep need and excessive daytime sleepiness when assessed only by subjective means, emphasizing the unreliability of self-assessment of increased sleep propensity in traumatic brain injury patients. At polysomnography, slow wave sleep after traumatic brain injury was more consolidated. The most important risk factor for developing increased sleep need after traumatic brain injury was the presence of an intracranial hemorrhage.

In conclusion, we provide controlled and objective evidence for a direct relation between sleep-wake disturbances and traumatic brain injury, and for clinically significant underestimation of posttraumatic sleep-wake disturbances by trauma patients.

Introduction

Sleep-wake disorders (SWD) are frequent following acute traumatic brain injury (TBI) and impair quality of life in TBI patients. Several studies highlighted the high prevalence of excessive daytime sleepiness (EDS) and increased sleep need after TBI (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007; Castriotta et al., 2007; Chaumet et al., 2008; Guilleminault, Faull, Miles, & van den Hoed, 1983; Masel, Scheibel, Kimbark, & Kuna, 2001; Ouellet & Morin, 2006; Parcell, Ponsford, Rajaratnam, & Redman, 2006; Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013; Schreiber et al., 2008). In a recent meta-analysis of 21 clinical studies, approximately 50% of TBI patients suffered from posttraumatic SWD: increased sleep need per 24 h and EDS were among the most common and disturbing posttraumatic SWD (Mathias & Alvaro, 2012). However, the reported prevalence of posttraumatic SWD varies considerably. This is because the presently available studies differ significantly regarding study design (mostly retrospective studies), assessment of sleep problems (questionnaires vs. sleep laboratory examinations) and inconsistent definitions of SWD resulting in a considerable variance regarding prevalence of SWD after TBI. To address the problem of heterogeneous definitions of SWD, we recently introduced the term "posttraumatic pleiosomnia" for increased sleep need following TBI (Sommerauer et al., 2013). Earlier, this symptom was referred to as posttraumatic hypersomnia, but the concept of hypersomnia comprises both increased sleep need per 24 h and EDS (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2005) and is therefore misleading, particularly for TBI patients who may suffer from either EDS or excessive sleep need or from both (Baumann et al., 2007).

The pathophysiology of EDS and pleiosomnia after TBI remains elusive. However, fatal TBI is associated with a partial loss of wake-promoting hypocretin (orexin)-producing neurons (Baumann et al., 2009). This suggests that damage to hypothalamic neurons and to other wake-promoting neuronal populations might be associated with posttraumatic EDS and pleiosomnia, but there are no acute biomarkers to predict the evolution of these SWD. For instance, it has not been examined whether acute dysfunction in neuro-endocrine pathways involving the hypothalamic-pituitary-adrenal axis is related to the development of increased sleep propensity after TBI.

In this study, we examined the prevalence and electrophysiological characteristics of posttraumatic EDS and pleiosomnia in a prospective and controlled approach by systematically examining TBI patients 6 months after injury with both subjective and objective sleep measures in comparison to an age- and gender-matched control group. Furthermore, we tested whether sleep was more consolidated after TBI and whether TBI was associated with a relative increase in EEG power density in the delta range. These analyses were motivated by the hypothesis, that increased

slow-wave activity might be linked to neuronal recovery (Carmichael & Chesselet, 2002; Stickgold, Hobson, Fosse, & Fosse, 2001; Tononi & Cirelli, 2006). As secondary endpoint, we correlated neuroimaging and laboratory measures reflecting neuronal damage in general, and more specifically dysfunction in the hypothalamic-pituitary-adrenal axis in the acute phase of TBI with the occurrence of posttraumatic SWD, to identify potential early predictors of posttraumatic EDS and pleiosomnia.

Methods

The protocol for this clinical study was approved by the local ethics committee (*Kantonale Ethikkommission Zurich*). Written informed consent for study participation was obtained from all patients and healthy controls before participation.

Study design

This is a prospective controlled trial to examine the prevalence, severity, and natural history of SWD after TBI in relation to severity of trauma (Glasgow Coma Scale), presence of brain damage (intracranial hemorrhage), and selected neurochemical biomarkers. Patients were examined at two time points: (i) in the acute phase after TBI for clinical staging, brain computed tomography (CT) scan and laboratory assessment, and (ii) 6 months after TBI for a detailed analysis of sleep and wakefulness (2-week actigraphy, followed by nocturnal video-polysomnography and multiple sleep latency tests, MSLT) and follow up laboratory assessment (Fig. 1).

Participants

Between July 2009 and June 2012, we screened 140 patients with acute, first-ever TBI admitted to our hospital and included 60 patients. Patients with prior TBI, other neurological or systemic diseases, drug or alcohol abuse, or psychiatric comorbidities were excluded.

For the analyses of sleep and wakefulness, we enrolled an age- and gender-matched healthy control group without prior TBI. For this purpose, we prospectively searched for controls by word-of-mouth advertising. To achieve optimal controlling of the sleep-wake outcome measures, we introduced a novel strategy for matching the control group: In order to get similar extents of sleep satiation before sleep laboratory examinations, we matched for the difference of total sleep times on actigraphy between working days and weekends/holidays, because this difference

reflects chronic sleep restriction during workdays. By this additional matching, we could therefore rule out a possible bias in the assessment of sleep measures due to chronic sleep restriction. Both after screening and again after sleep-wake assessments in the sleep laboratory, participants with SWD including circadian rhythm disorders on actigraphy were excluded as controls. Furthermore, volunteers with neurological disorders, a history of SWD or psychiatric illnesses were excluded, as well as parents with young children or subjects on shift work. To get a representative rather than an artificial control sample (Mignot et al., 2006) , apnea-hypopnea indexes (AHI) from 5 to 15 on polysomnography or mean sleep latencies from 5 to 8 min on multiple sleep latency test (MSLT) were accepted for inclusion as control if no subjective EDS was indicated by the Epworth Sleepiness Scale (ESS). Sleep laboratory examinations in controls were performed only once. Six controls were included in a previous study (Sommerauer et al., 2013).

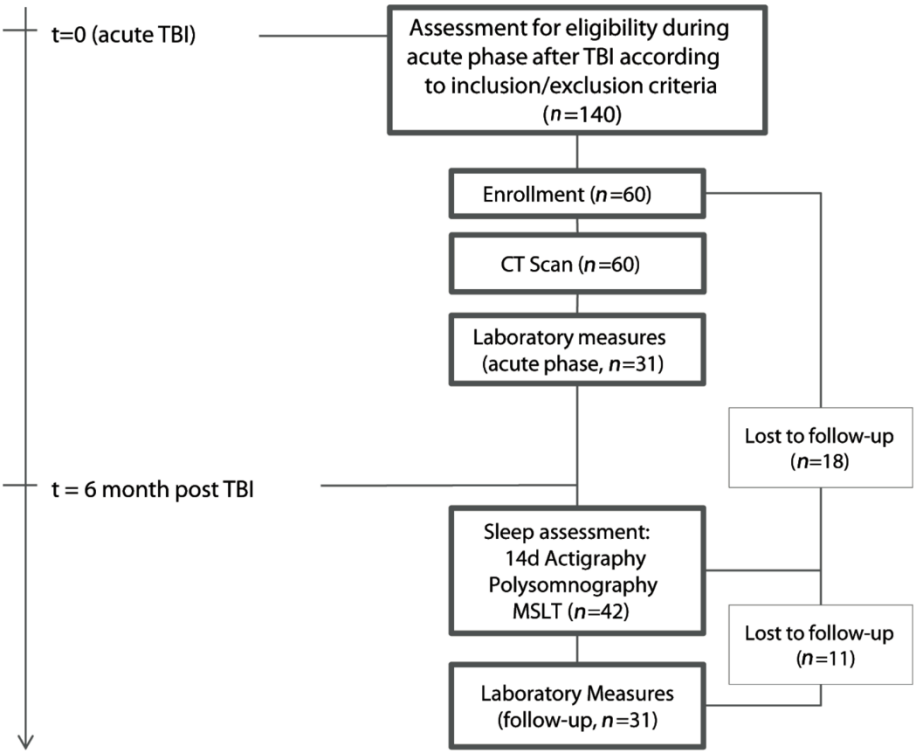

Figure 1 - Overview on study design and patient enrollment. Explanations for loss to follow-up are given in the results section of the manuscript. CT: computed tomography; MSLT: multiple sleep latency test.

Examinations in the acute phase after traumatic brain injury

We categorized the severity of TBI using the Glasgow Coma Scale (13–15: mild, 9–12: moderate, and 3–8: severe) on admission to the hospital. Furthermore, we performed a CT scan within the first 4 h after trauma to estimate severity and localization of brain injury.

Laboratory examinations within the first 5 days after trauma included the assessments of the hypothalamic-pituitary-adrenal axis (adrenocorticotropic hormone, cortisol, and aldosterone, adrenaline, noradrenaline, dopamine), and of serum biomarkers reflecting neural injury and indicating poor overall recovery after TBI (S100 calcium binding protein B, S100B, and neuron-specific enolase, NSE; Berger et al., 2002; Lamers et al., 2003; Vos et al., 2004). The rationale to screen for hormonal disturbances in TBI patients as possible predictors of sleep-wake disturbances was based on the hypothesis that shearing injuries may cause loss of hormone-releasing neurons in the brainstem and hypothalamus, and would possibly result in the disruption of neuro-endocrine pathways, similarly as it has been shown for orexin-producing neurons after TBI (Baumann et al., 2009). The same blood tests were performed again 6 months after TBI.

Assessment of sleep-wake disturbances 6 months after traumatic brain injury

We screened for changes in sleep habits, sleep quality, daytime vigilance and insomnia by detailed and structured interviews. Patients and controls completed validated questionnaires such as the Epworth sleepiness scale, the Sleep Apnea Scale of the Sleep Disorders Questionnaire, the Ullanlinna Narcolepsy Scale and the Fatigue Severity Scale. We further investigated psychological mood, fatigue, quality of life using reliable and widely used self-report measures and the "Allgemeine Depressionsskala" (ADS) to assess depressive symptoms (Hautzinger & Bailer, 1993).

To screen for circadian SWD and to quantify sleep need per 24 h, patients and controls were examined with sleep logs and wrist actigraphy (Actiwatch, Neurotechnology; King, Jaffre, Morrish, Shneerson, & Smith, 2005). Wrist actigraphy was recorded and analyzed as described before (Cippà et al., 2013).

Thereafter, we performed overnight video-polysomnography from 11 p.m. to 7 a.m. as described previously (Baumann et al., 2007). Sleep-stage scoring was performed visually according to revised international criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007) and sleep stage distribution was assessed by calculating the relative time in each sleep behavioural state. and sleep stage distribution was assessed by calculating the relative time in each sleep behavioral state. For

further signal processing of the raw data, we used MatLab (The MathWorks Inc., Natick, MA, 2009). We calculated delta power in slow-wave sleep as follows: First, all 30s-epochs that were scored as NREM3 were included. This dataset was then subdivided into epochs of 5s length. Artefacts were rejected by an automated dual algorithm based on a short-term kurtosis measure (mainly for electrode artefacts) and spectral information (e.g. movement artefacts). Fast Fourier Transformation was then applied on each 5s-epoch after multiplication by a Hann window to address the problem of edge discontinuities (zero padding was used to expand the signal in each 5s-epoch of 500 data points to a window size of 512 points). For better comparability between subjects, the calculated delta power (0.5-4.5Hz) was normalized to the total spectral power (1-50Hz) for each individual. To calculate a quantitative measure of sleep fragmentation, we first assessed the total number of behavioral state bouts. A behavioral state bout was defined as a consecutive series of epochs in the same behavioral state without state transitions. The resulting amount of behavioral state bouts was then divided by the total number of 5s-epochs in the same sleep stage. The resulting sleep fragmentation index reflects therefore the relative number of behavioral state bouts per time (e.g. highly fragmented sleep with many changes in sleep-wake behavioral states will result in a high sleep fragmentation index). We chose 5s-epochs for this analysis because the artifact rejection algorithm was based on this time interval, but sleep stage classification was based on the classical 30s epoch length (Iber et al., 2007).

Objective EDS was assessed by standardized MSLT. Briefly, the procedure entails 4 opportunities for sleep lasting 20 min every 2 h; subjects were told to relax, and sleep was permitted. Sleepiness was then assessed by mean sleep latencies as derived from the concurrent EEG in the absence of external alerting factors. Mean sleep latencies below 8 min were considered to represent objective EDS (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2005).

Statistical analyses

We used means, proportions and quartiles for descriptive comparative analysis of continuous data. TBI patients and controls were compared with unpaired 2-sided t-tests and data from TBI patients at different time points with paired t-tests. More than two groups were compared by One-Way ANOVA. We used $\chi 2$-statistics to compare nominal data. To compare objective and subjective EDS (i.e. comparison between MSLT vs. ESS), we used McNemar's test to account for marginal homogeneity (i.e. to test the null hypothesis whether subjective and objective assessment do not differ significantly). Bivariate correlation analysis was done by calculation of Pearson's

correlation coefficient to reveal significant relations between clinical characteristics or endocrine markers with sleep outcome measures.

Furthermore, we performed a subgroup analysis for the TBI patients with respect to severity of TBI (mild versus severe TBI) and compared the 2 groups by One-Way Anova. For all analyses, 2-tailed p values < 0.05 were considered to be significant.

Results

Of 140 screened patients, 33 were excluded because of substance abuse or neurological, sleep–wake or psychiatric disorders prior to TBI, and 47 patients denied to participate, resulting in a cohort of 60 TBI patients (range 18-71 years, 74% male). Forty-two out of these patients with first-ever traumatic brain injury and no prior SWD were available for follow-up examinations 6 months after TBI (Fig. 1). After acute phase examinations, 18 participants were lost to follow-up for various reasons (new onset of severe TBI-unrelated disease: n = 1, work: n = 2, moved to a foreign country: n = 2, socioeconomic problems: n = 1, new onset epilepsy: n = 1, no reason given: n = 11). Except for one subject in the severe TBI group, all TBI patients had ADS scores below the cut-off of 23, indicating that all but one TBI patients did not suffer from clinical depression. Thirty-one of 42 patients with full sleep laboratory assessments had complete serum laboratory results in both the acute and the 6-month phase.

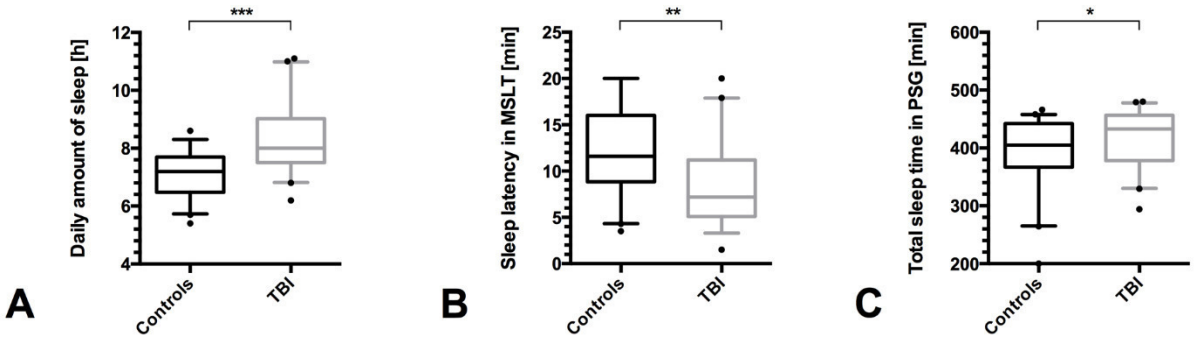

Figure 2 - Sleep amount and sleep latency in traumatic brain injury (TBI) patients and healthy controls. (A) Daily hours of sleep as measured by continuous actigraphy over 2 weeks, showing an increase of 1.2h in total amount of sleep / 24h in TBI patients as compared to the control group. (B) Mean sleep latencies on multiple sleep latency test (MSLT) in TBI patients are 28% lower than in healthy controls. (C) Total sleep time in PSG reveals an increased amount of sleep for TBI patients in 8h polysomnography. Box plots indicate means (horizontal line), upper and lower quartiles (box) and extrema (whiskers), outliers are shown as black dots. *** = $P < 10^{-6}$ ** = $P < 0.0001$ * = $P < 0.05$

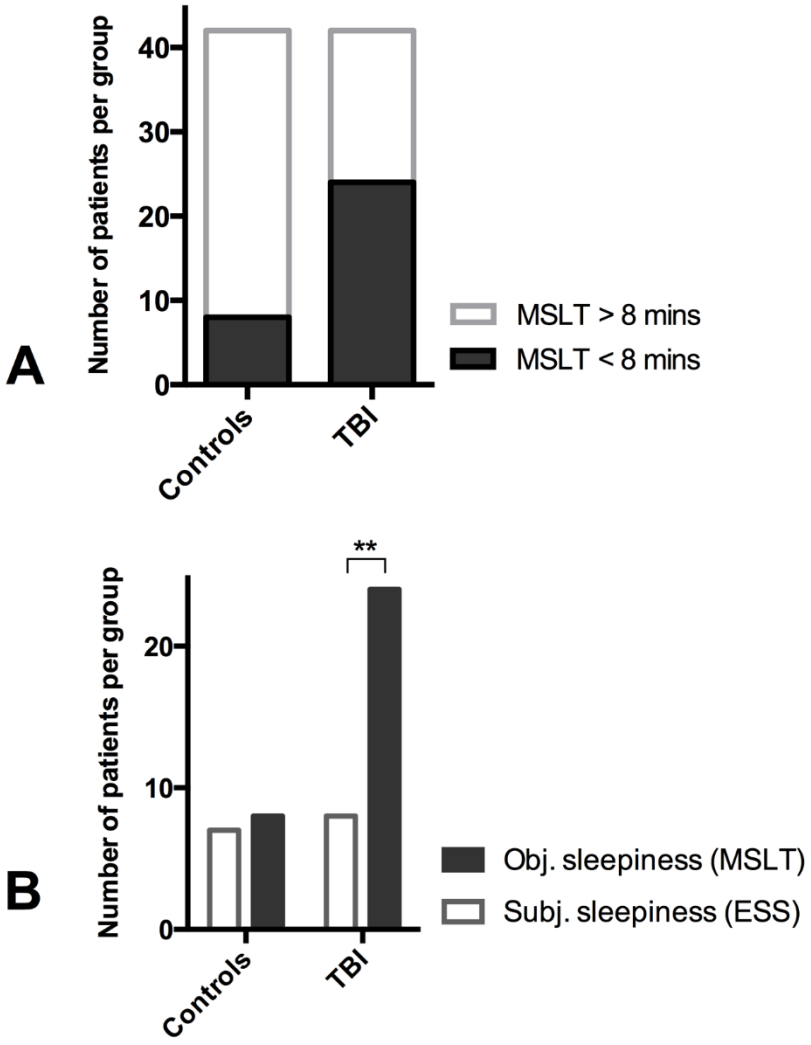

Figure 3 - Objective vs. subjective excessive daytime sleepiness (EDS) in traumatic brain injury (TBI) patients and controls. (A) Objective excessive daytime sleepiness (defined as average sleep latency < 8min on MSLT, *dark grey*) was found in 24/42 TBI patients (57%) as compared to 8/42 healthy subjects (19%; odds ratio: of 5.6, $P < 0.001$) (B) Comparison of subjective EDS (based on Epworth sleepiness scale, *white*) and objective EDS (based on multiple sleep latency test, *dark grey*). In healthy controls, no difference between subjective and objective measures was found, but in TBI patients, EDS was 3 times more prevalent when assessed objectively (McNemar objective vs. subjective EDS: $P > 0.99$ in controls and $P < 0.0005$ ** in TBI patients).

Post-traumatic pleiosomnia and excessive daytime sleepiness

Continuous actigraphy assessment over 2 weeks confirmed pleiosomnia in TBI patients: we found that TBI patients slept 1.2 h more per 24 h (8.3 ± 1.1 h, mean ± SD) than controls (7.1 ± 0.8 h, mean ± SD, t-test: $P < 0.0001$, Fig. 2A). On MSLT, average sleep latency was 12.1 ± 4.7 min in

controls and 8.7 ± 4.6 min in TBI patients (t-test: $P < 0.001$, Fig. 2B). Total sleep time in PSG was significantly longer in TBI patients (392 ± 10 min in controls and 419 ± 7 min in TBI patients, t-test: $P < 0.05$, Fig. 2C). Objective EDS (defined as a mean sleep latency < 8 min) was found in 57% of TBI patients as compared to 19% in healthy subjects (Fig. 3A, $\chi 2$ test: $P = 0.001$, Cramer's φ: 0.39), resulting in an odds ratio of 5.6 (confidence interval: 2.1-15.1) for TBI patients versus healthy controls (Fig. 3A). Other causes than TBI of increased EDS and pleiosomnia such as sleep apnea insufficient sleep syndrome were not present (no difference between groups, Table 1). TBI patients did not show signs of circadian dysfunction in actigraphy.

Sleep state misperception after traumatic brain injury

Subjective EDS and fatigue were assessed by the Epworth sleepiness scale and the fatigue severity scale, and subjective sleep time per 24 h by sleep logs. Although objective EDS and sleep need per day differed significantly between patients and controls, we found no significant differences of these subjective measures between the 2 groups (Table 2, Fig. 3B). Similarly, when comparing the objective against subjective EDS evaluation, we found no significant differences for controls, whereas in TBI patients objective EDS was markedly more pronounced than recorded by subjective assessment (Fig. 3B, McNemar objective vs. subjective: p-values > 0.99 in controls and 0.0004 in TBI patients). In other words, 8 of 42 TBI patients (19%) reported subjective EDS, but objective EDS was detected in 24 of 42 patients (57%, $P < 0.0005$). Similarly, sleep logs in controls showed no difference in sleep times between sleep logs and actigraphy, but in TBI patients, sleep times were underestimated by sleep logs when compared to actigraphy results ($P = 0.002$, Table 1).

Consolidated slow-wave sleep in traumatic brain injury patients

Next, we addressed the question whether objective EDS and pleiosomnia in TBI patients are related to changes of sleep architecture or delta power of deep slow wave sleep (NREM3) during polysomnography. Consolidation of sleep was assessed by calculation of a sleep fragmentation index based on manual sleep scoring (see Material/Methods). This measure represents the average number of behavioral state bouts per time (thus lower values indicate a more consolidated sleep). In TBI patients, NREM3 but also NREM1 and NREM2 sleep were significantly more consolidated (lower number of sleep bouts per time) than in controls, whereas REM sleep was not altered (Fig. 4, t-test: $P = 0.002$ for total effect). For the wake state, on the other hand, we observed a higher fragmentation index in TBI patients. Thus, whereas NREM sleep was more

consolidated after TBI, the wake state showed a higher instability. These findings are in line with a trend towards a higher amount of normalized delta power (0.5-4.5Hz) in TBI patients that resulted in a 22% increase in delta power (normalized delta power 0.44 in controls and 0.54 in TBI patients, t-test: P = 0.1, data not shown). Similarly, we also found less wake after sleep onset in the TBI group during Polysomnography (PSG), although this finding did not reach statistical significance (Table 1). Global sleep architecture as measured by relative sleep stage distribution showed no significant difference (Table 1).

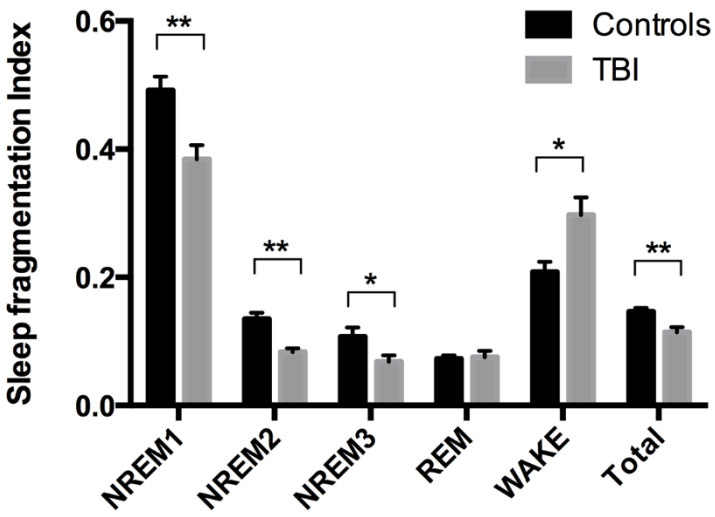

Figure 4 - Sleep fragmentation of traumatic brain injury patients and controls. Sleep fragmentation (number of sleep bouts / time) is reduced in non-rapid eye movement (NREM) sleep in TBI patients (*grey*) as compared to controls (*black*), whereas fragmentation of REM sleep did not differ (t-test: ** = P < 0.005, * = P < 0.05).

Severe trauma and intracranial haemorrhage as risk factors for pleiosomnia

To identify predictors or risk factors for posttraumatic SWD, we compared the sleep-wake outcome measures with clinical and imaging TBI characteristics in the acute phase. Correlation analysis revealed a strong dependence of pleiosomnia on low initial GCS, i.e. high TBI severity, and on hemorrhage as assessed by CT scans. Pearson's bivariate correlation coefficients were R = 0.46 (P = 0.003) for pleiosomnia vs. initial GCS and R = 0.42 (P = 0.005) for pleiosomnia vs. presence of intracranial hemorrhage (statistically controlled for age and gender, Figs 5A/D, full correlation not shown). Occurrence and extent of pleiosomnia was not associated with size or location of intracranial bleeding. Other clinical measures such as age or gender had no influence on sleep-wake outcome. In a subgroup analysis, the sleep amount in the hemorrhage TBI group

differed significantly from controls, as well as from the non-hemorrhage TBI group (Figs 5A,C), whereas in TBI patients without intracranial hemorrhage the increased sleep amount was not significantly different from controls. Mean sleep latency on MSLT, on the other hand, was decreased in all TBI patients and did not differ between patients with or without intracranial hemorrhage (Fig. 5B). Similarly, the subgroup analysis for low severity and high severity TBI based on initial GCS revealed again that pleiosomnia depends on TBI severity and differed between high and low grade TBI patients, whereas objective EDS was independent from the initial GCS on hospital admission (Figs 5 D-F).

Correlation of sleep-wake outcome with acute phase laboratory markers

To find neurochemical predictors of posttraumatic sleep-wake outcome, we assessed whether sleep-wake changes 6 months after trauma were related to the presence of serum TBI markers, or to pathological levels of hypothalamo-pituitary-adrenal hormones in the acute phase after TBI. In a first step, we compared these acute laboratory measures with follow-up values at the time of sleep evaluation (6 months after TBI). Trauma markers such as NSE and S100B were elevated in the acute phase (Fig. 6A), but had no predictive value for sleep-wake outcomes. In terms of neuroendocrine parameters, only adrenaline levels were significantly elevated (Fig. 6A). Overall cortisol levels were not changed, but we observed a change of the diurnal cortisol pattern: In the acute phase, the circadian gradient between morning and afternoon cortisol was flattened, as compared to the normal more pronounced difference between a.m. and p.m. cortisol levels 6 months after TBI (Fig. 6B). Next, we compared these neurochemical markers with sleep-wake outcome parameters in a bivariate correlation analysis and we found that decreased morning cortisol levels in the acute phase correlated significantly with objective EDS 6 months after TBI (Fig. 6C, $R = 0.88$, $P = 0.005$, $n = 10$).

Table 1 – Demographical data for TBI patients and controls

	Controls	TBI	p-value
Population characteristics			
Age	36.5 ± 13.2	35.5 ± 14.4	0.84
Gender (m/f)	31/11	31/11	n.a.
Polysomnography			
Total Sleep Time [min]	392 ± 10	420 ± 7	0.04
Sleep Efficiency	87.6 ± 2 %	87.9 ± 1.3 %	0.98
Sleep Latency (NREM2) [min]	31.9 ±6.7	23.7 ± 2.8	0.27
Wake after Sleep Onset [min]	11.4 ± 1.7	8.2 ± 1.1	0.17
Arousal Index	7.7 ± 0.8	6.0 ± 0.6	0.09
PLMS Index	1.3 ± 0.6	2.7 ± 1.2	0.30
AHI	3.2 ± 1	2.3 ± 0.5	0.42
ODI	3.3 ± 1	2.2 ± 0.4	0.32
NREM1	9.1 ± 0.7	9.9 ± 1.2 %	0.06
NREM2	41.2 ± 1.4	43.9 ± 1.3 %	0.32
NREM3	20.2 ± 1.2	20.1 ± 1.0 %	0.29
REM	18.1 ± 0.9	18.0 ± 1.0 %	0.43
WAKE	11.4 ± 1.7	8.2 ± 1.1 %	0.49
Actigraphy			
Sleep Time /24 h (actigraphy)	7.1 ± 0.8 #	8.3 ± 1.1 *	$P < 0.00001$
Sleep Time / 24 h (sleep log)	7.3 ± 1.1 #	7.5 ± 1.4 *	n.s
Difference WD/WE	0.4 ± 0.8	0.5 ± 0.8	n.s.

PLMS: Periodic limb movements during sleep. *AHI*: Apnea-hypopnea index. *ODI*: Oxygen desaturation index. Relative amounts of sleep stages are given in percentage of total time in bed for non-rapid eye movement sleep stage 1 (NREM1), NREM2, NREM3, REM sleep, and wakefulness. *Sleep Time /24 h (Actigraphy)*: Time asleep as measured by actigraphy recordings. *Sleep Time / 24 h (Sleep log)*: Time asleep per 24 h as assessed by sleep logs. *Difference WD/WE*: Difference of daily hours of sleep between weekdays and weekends. P-values are given for comparison of controls versus TBI patients. Sleep time per 24 h as assessed objectively by actigraphy and sleep time per 24 h as reported on sleep logs did not differ in controls (#, n.s), whereas sleep times were subjectively underestimated in TBI patients (* = $P < 0.005$, paired t-test).

Table 2 – Subjective sleep measures for TBI patients and controls.

	TBI	CONTROLS	p-value	stat
ESS	6.1±3.1	5.6±3.3	0.64 (n.s.)	t-test
FSS	3.0±1.1	2.7±1.3	0.23 (n.s.)	t-test
Ullanlinna	7.0±3.5	6.2±3.2	0.42 (n.s.)	t-test
SNS	17.5±17.0	22.6±13.2	0.54 (n.s.)	t-test
Sleepiness y/n	16	10	0.15 (n.s.)	Chi-Square
SWD y/n	12	10	0.61 (n.s.)	Chi-Square
ESS > 10	8	7	0.77 (n.s.)	Chi-Square

ESS: Epworth sleepiness Scale, *FSS*: Fatigue Severity Scale, *Ullanlinna*: Ullanlinna Narcolepsy Scale. *SNS*: Swiss Narcolepsy Score. *Sleepiness y/n*: Overall subjective assessment of daytime sleepiness. *SWD y/n*: Overall subjective assessment of the presence of a sleep-wake disorder.

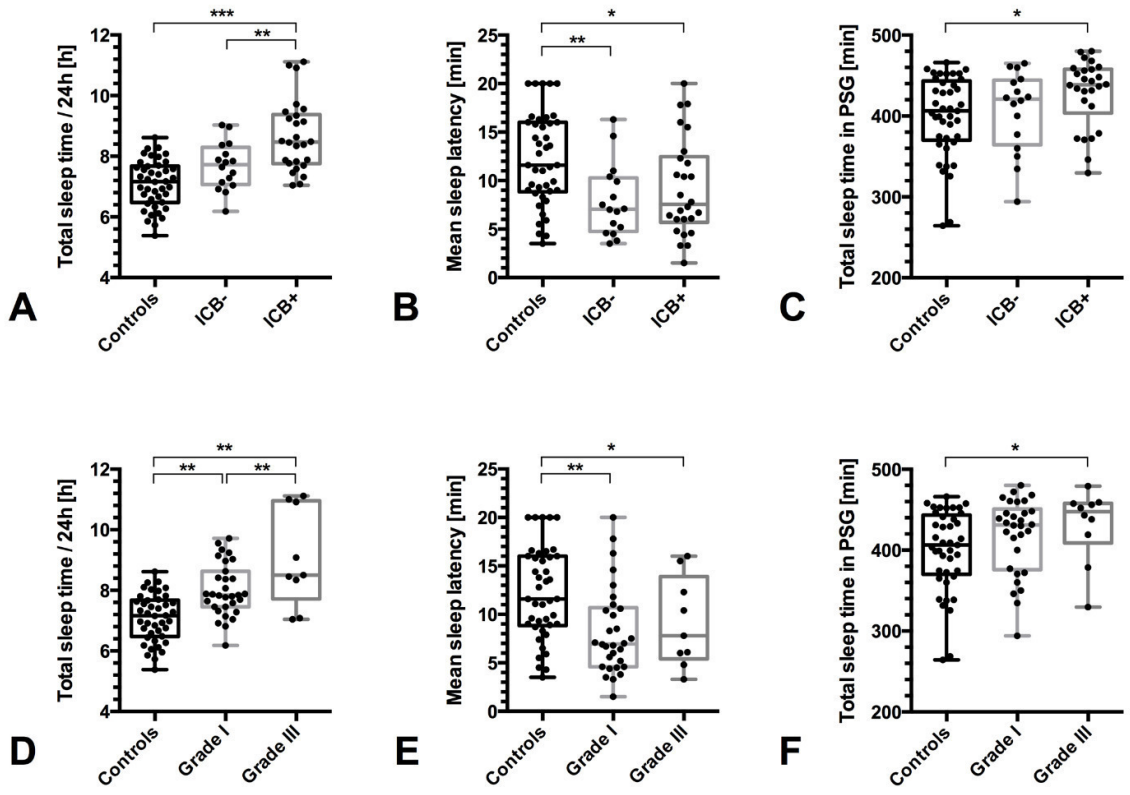

Figure 5 - Pleiosomnia and excessive daytime sleepiness with respect to occurrence of intracranial hemorrhage and traumatic brain injury (TBI) severity. (A) Patients with intracranial hemorrhage (ICB+) had significantly more sleep per 24h than both controls and TBI patients without bleedings (ICB-). Pearson correlation: $R = 0.604$, $P < 0.001$. (B) Mean sleep latencies on MSLT differed between controls and TBI patients, but no significant difference was observed between TBI patients with (ICB+) and without (ICB-) intracranial bleeding (Pearson correlation: $R = -0.292$, $P < 0.01$). (C) Patients with intracranial hemorrhage (ICB+) showed increased total sleep time in PSG, whereas sleep time in patients without hemorrhage (ICB-) did not differ from the control group. (D) Patients with high severity TBI (GCS≤8) had more sleep per 24h than both controls and low severity TBI patients (GCS≥13). (E) Mean sleep latencies on MSLT differed between controls and TBI patients, but not between TBI patients low and high severity trauma. (F) Patients with grade III TBI had elevated total sleep time in PSG as compared to controls. (*** = $P < 0.001$, ** = $P < 0.01$ * = $P < 0.05$ in One-Way ANOVA, n = 84).

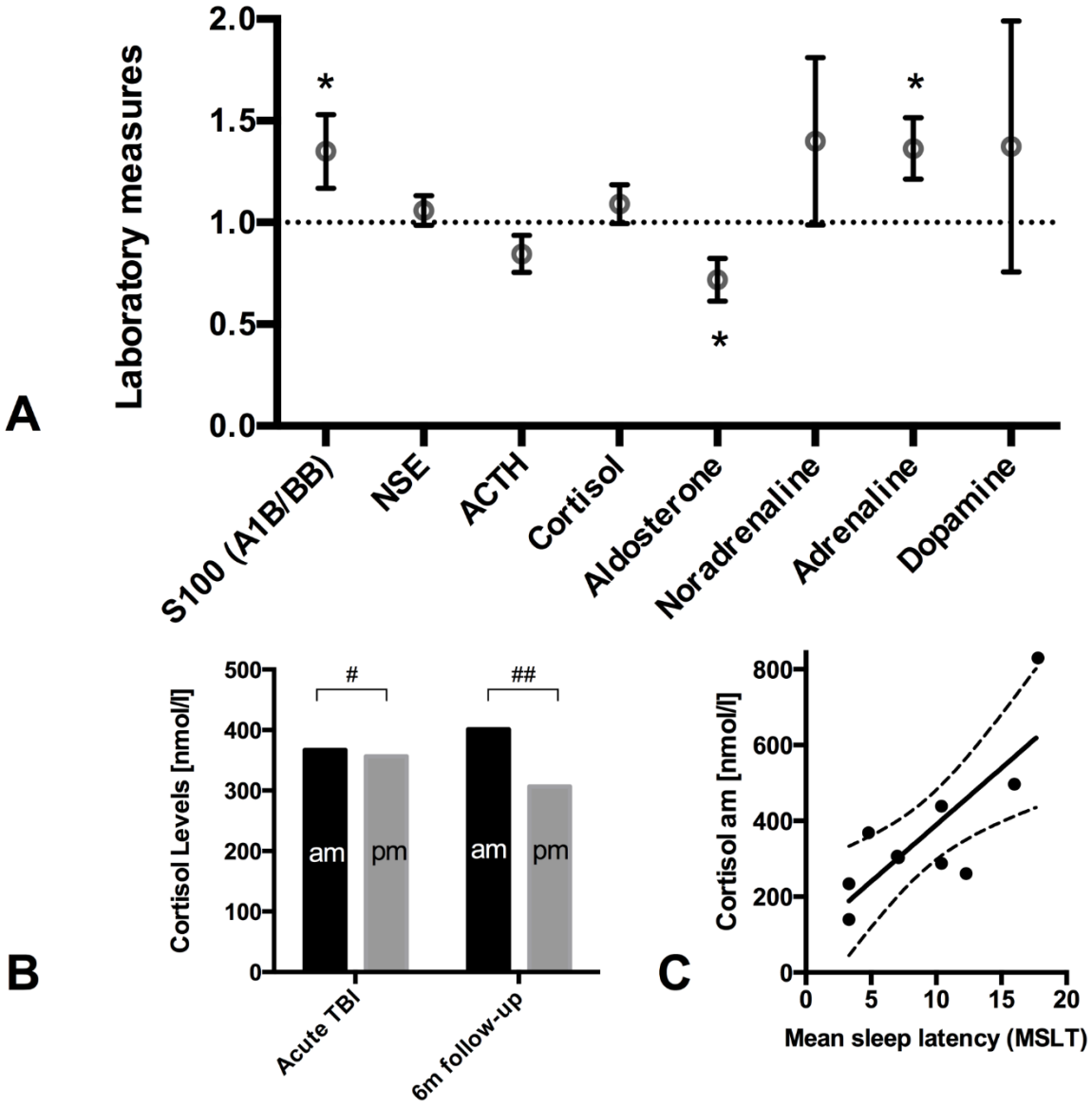

Figure 6 - Levels of potential biomarkers in the acute phase vs. follow-up after traumatic brain injury (TBI). (A) Acute phase lab values (within 5 days after TBI, grey circles) normalized to values at follow-up (6 months after TBI, dotted line) revealed increased values for TBI markers (S100) and elevated adrenaline levels (* $P < 0.05$). (B) Change of the diurnal cortisol pattern: The difference between a.m. (black) and p.m. (grey) cortisol levels was diminished in the acute phase (# $P = 0.44$ for comparison acute vs. 6 months, paired 2-sided t-test) as compared to 6 months after TBI (## $P = 0.06$ for comparison acute vs. 6m, un-paired one-sided t-test). (C) Morning cortisol levels (cortisol am) in the acute phase correlated significantly with sleepiness as measured by multiple sleep latency tests (MSLT) 6 months after TBI ($R = 0.88$, $P = 0.005$, $n = 10$). S100: S100 calcium binding protein; ACTH: adrenocorticotropic hormone; NSE: neuron-specific enolase.

Discussion

We present the first prospective and controlled clinical trial to examine EDS and pleiosomnia - i.e. excessive sleep need - in TBI patients by objective and subjective sleep measures. Six months after TBI, we found a marked increase of objective EDS and clinically relevant pleiosomnia as compared to an age- and gender-matched control group. Polysomnography revealed that NREM sleep in TBI patients is more consolidated than in controls, but the relative distribution of sleep stages is not different. The observed increase in total delta power after TBI was not significant in our sample. In contrast to these objective findings, TBI patients appear to underestimate both EDS and pleiosomnia if only subjective measures such as sleep logs or sleep questionnaires are applied.

The observed prevalence of posttraumatic EDS (57% of TBI patients) is in line with previous uncontrolled or retrospective trials (Baumann et al., 2007; Castriotta et al., 2007; Masel et al., 2001), and the observed prevalence of EDS in controls is in general agreement with earlier findings in large community-based cohort studies (Mignot et al., 2006). Our control group was not only matched for age and gender, but also for difference of total sleep times on actigraphy between working days and weekends/holidays, i.e. for overall sleep satiation before polysomnography and MSLT. By controlling for this measure, we were able to compare objective sleep-wake measures between groups without a potential bias due to chronic sleep deprivation. Furthermore, by including also subjects with sleep latencies < 8 min as controls, we were able compare TBI patients to a reliable and not overly preselected healthy reference group, because moderate objective daytime sleepiness is a frequent finding in healthy subjects (Mignot et al., 2006). This was also the reason why we matched controls for the extent of sleep satiation before sleep laboratory examinations. By doing this, we confirm a significantly increased prevalence of EDS and of pleiosomnia and conclude – in the absence of other potential causes of SWD - that these are probably directly related to the trauma. A potential confounding factor is the occurrence of depression after TBI and development of secondary posttraumatic SWD (e.g. insomnia). However, standardized neuropsychiatric assessment revealed that only one TBI patient had scores suggestive for a clinical depression. Therefore, we conclude that EDS and pleiosomnia in this cohort of TBI patients is not caused or worsened by accompanying mood disorders.

Pleiosomnia was strongly correlated with both severe TBI as assessed with GCS and with the presence of an intracranial hemorrhage upon CT scan in the acute phase after TBI. This indicates that trauma patients with an objective correlate of severe TBI, i.e. intracranial bleedings, are more susceptible to developing posttraumatic pleiosomnia. Other clinical parameters such as age or gender had no influence on the development of posttraumatic pleiosomnia. Furthermore, as SWDs

were not associated with size or localization of bleedings, we suggest that intracranial hemorrhage itself is not the origin for poor sleep-wake outcome, but rather a mere indicator for the severity of the trauma. We rather hypothesize that patients with severe trauma may suffer more often from direct or secondary lesions in the hypothalamus or rostral brainstem, which are not accessible by CT scan. This might lead to the otherwise observed loss of wake-promoting neuronal systems with TBI, which could explain the occurrence of pleiosomnia. On the other hand, we cannot exclude the possibility that other mechanisms that are related to intracranial hemorrhage – such as vasospasms that may affect cerebral blood flow to the midbrain – might contribute to increased sleep need. However, given the fact that recordings were made 6 months after trauma, such mechanisms are likely to be less relevant. These deductions however, lie beyond the scope of the current study and more detailed (MRI-based) neuroanatomical analyses in TBI patients are needed to investigate the occurrence and distribution of micro-lesions in the brainstem after TBI.

On the other hand, we might speculate whether increased sleep need might be associated with the need for neuroplasticity after TBI. It has been shown that synchronous slow wave EEG activity is associated with neuronal plasticity or synaptic strength, both during sleep and in the awake state (Carmichael & Chesselet, 2002; Stickgold et al., 2001; Tononi & Cirelli, 2006). Our finding of more consolidated deep sleep and a tendency towards higher delta power in NREM sleep might be in favor of such a hypothesis. Sleep architecture (as reflected by the percentage breakdown of sleep stages) was unaltered in TBI patients as compared to healthy controls. In other words, TBI patients are in need for longer overall sleep times, but still have the same relative amounts of sleep stages. Altogether, our findings indicate that patients with more severe TBI and possibly higher levels of cellular or axonal damage might be in need for longer sleep times per 24 h and for more consolidated slow wave sleep with higher delta power. In this regard, it would be interesting to learn whether slow wave sleep with increased delta power is even more accentuated early on after TBI. This question could be addressed by further studies.

We diagnosed pleiosomnia based on actigraphy recordings. It must be noted that decreased levels of activity might have led to an overestimation of sleep times per 24 h. This is why we double-checked actigraphy data with the sleep logs that have been filled by the patients during actigraphy recordings. Furthermore, sleep laboratory examinations in a controlled setting (MSLT, PSG, Figs 2 B/C) confirmed the occurrence of increased sleep need in TBI patients. However, maximal sleep time at PSG was limited to 8 h, which leads to a quantitative underestimation of sleep need per 24 h especially in subjects with increased sleep need (>8 h). Therefore and despite the given methodological limitations, we believe that actigraphy delivers better insights into total average sleep time per 24 h.

Posttraumatic EDS, on the other hand, occurs independently of traumatic intracranial hemorrhage and trauma severity. In our population, many patients with minor head trauma still developed clinically relevant EDS. Therefore other factors than direct neuronal damage might influence posttraumatic EDS. In this line, analysis of neuro-endocrine markers revealed that flattened diurnal cortisol profiles and low a.m. cortisol levels correlate with the development of posttraumatic EDS, i.e. shorter sleep latency on MSLT. Impaired alertness (Chapotot, Gronfier, Jouny, Muzet, & Brandenberger, 1998) and awakening problems have been reported in patients with lowered cortisol levels (Dijk et al., 2012). Thus, pathological cortisol signaling appears heralding a subsequent evolution of midbrain-driven EDS. Earlier studies have suggested that midbrain structures are particularly vulnerable to TBI (Baumann et al., 2009; Crompton, 1971). Considering our findings, it appears that even mild TBI can lead to a relevant disturbance in the central regulation of the hypothalamic-pituitary-adrenal axis without any further brain damage or focal neurological deficits.

However, as an important limitation, this study was not designed to account for diurnal cortisol changes. The analysis of a.m. and p.m. levels was done post-hoc and therefore the correlation analysis was done only for patients in whom a.m. and p.m. cortisol was available. Therefore, no conclusion for TBI patients in general can be drawn at this point and only future systematic approaches might reveal whether or not diurnal cortisol level measurements might be predictive of posttraumatic EDS.

Finally, many TBI patients with marked increase of objective EDS in MSLT did not report subjective EDS as assessed by various sleep questionnaires. The same applies for increased sleep need: pleiosomnia was obvious in TBI patients as compared to controls, but sleep logs revealed similar reported sleep times in both groups. In other words: although TBI patients presented with pronounced objective EDS and pleiosomnia, the applied subjective tests failed to capture both EDS and pleiosomnia. These results indicate a strong sleep state misperception in TBI patients. The reason for this striking difference between objective and subjective sleep measures remains unclear. As this study was not designed to assess for anosognosia in TBI patients, this question should be addressed in future studies by appropriate neuropsychological assessments. From a clinical point of view, this finding poses a diagnostic challenge, as standardized and validated screening instruments for sleepiness or hypersomnia (e.g. Epworth sleepiness scale, sleep logs, history-taking) obviously fail to detect SWD in TBI patients. Consequently, considering this data and forensic consequences of EDS (e.g. in patients driving motor vehicles), TBI patients should be examined with sleep laboratory examinations rather than self-reported sleep measures

whenever possible. As polysomnography is expensive and time-consuming, further studies might elucidate whether actigraphy and MSLT alone might be sufficient.

Acknowledgements

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4.5 Sleep-wake disorders persist 18 months after traumatic brain injury but remain underrecognized.

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Contribution: Sleep data acquisition and analysis.

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5 Discussion

The main aim of this thesis was (i) to assess whether electrophysiological and behavioral correlates of increased sleep pressure resulting from acute SD also apply to the condition of chronic SR. Further aims were (ii) to investigate potential underlying mechanisms of behavioral changes induced by chronic SR and (iii) to identify aspects of chronically increased sleep pressure in a clinical context. In the following sections the methods applied to address these aims and the findings relating to each of these aims will be discussed. Furthermore, limitations and implications for future research will be elaborated. Finally, an overall conclusion is provided in the last section.

5.1 Methodological considerations

The aims of this thesis were addressed in five research articles. Three of them are based on data acquired in a controlled, experimental, within-subject study with healthy individuals including the conditions of acute SD and chronic SR. The other two research articles are based on data acquired in a controlled, prospective clinical study in a patient population suffering from TBI. First, the experimental study will be discussed with regard to design and selected subject population. Next, advantages and limitations of the neuroscientific methods, i.e., the different high-density EEG assessments that were applied in this study will be elaborated. Finally, aspects regarding the clinical study design will be addressed.

5.1.1 Experimental study design

In our experimental study, healthy adults underwent the conditions of acute SD and chronic SR in a counter-balanced order. In total, 14 subjects were included in the study. As statistical power may be limited in a small sample size (J. Cohen, 1992), the relatively low number of subjects investigated constitutes the largest limitation inherent to the study design. However, assessing changes within instead of between individuals typically increases statistical power (Charness, Gneezy, & Kuhn, 2012). Furthermore, we aimed at reducing variability by selecting a sample that is as homogenous in as many characteristics as possible (e.g., age, gender, education, habitual sleep duration and sleep-wake rhythm). Additionally, the procedure in the sleep laboratory was highly standardized, including a strictly defined time schedule for testing sessions. A relatively long wash-out period between, and the control of sleep-wake times prior to both conditions was implemented to reduce the likelihood of carry-over effects. The findings obtained in our experimental study should definitely be replicated in a larger and more heterogeneous sample to

increase the extent to which they can be generalized. Nevertheless, the carefully elaborated study design allowed us to draw some (first) conclusions about the comparability between effects resulting from acute SD and chronic SR and about potential underlying mechanisms of behavioral changes after chronic SR.

We applied a multimodal approach, which allowed us to assess and to connect different aspects of sleep loss induced effects. The research articles presented in this thesis are based on a subpart of acquired measures. However, further analyses with regard to the remaining measures are ongoing and may allow us to connect even more aspects of sleep loss induced effects on behavior and brain functioning.

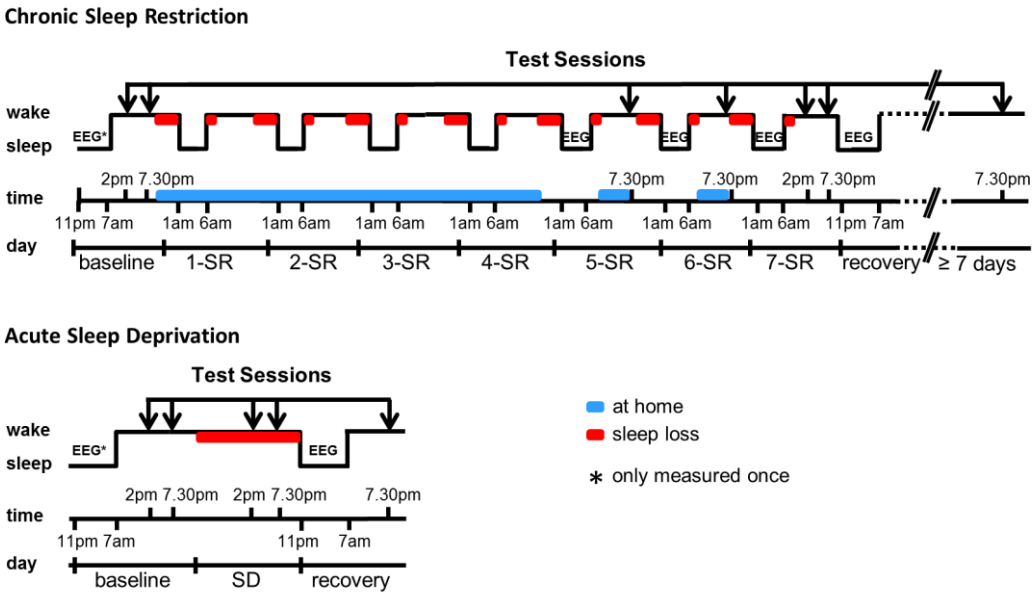

Figure 3 – Detailed experimental study design. All subjects underwent the chronic SR and acute SD in a controlled, counter-balanced order including 12 test sessions and 6 sleep EEG recordings for every subject in total. *The baseline night took place prior to the first sleep loss protocol (either prior SD or SR).

To assess acute SD and chronic SR induced effects, subjects underwent multiple test sessions and sleep assessments (Figure 3). The test sessions consisted of various behavioral tasks during which neural activity was recorded by high-density EEG. The behavioral tasks included the assessment of vigilance, working memory performance, financial risk-taking behavior, and financial and motor impulsivity. Every test session also included the recording of resting-wake EEG and the subjective assessment of sleepiness, mood and performance. Additionally, we applied single-pulse transcranial magnetic stimulation (TMS) in combination with high-density EEG (referred to as

TMS-EEG) in eight of our subjects in every test session (this method will be discussed in more detail in section 5.1.2). During the nights in the laboratory, all-night sleep was recorded by high-density EEG. At baseline, after the night of acute SD and after the last night of chronic SR, vigilance was assessed not only during the test sessions but every three hours to obtain an equally distributed vigilance profile over the whole day. Furthermore, saliva samples were collected every few hours during these days to assess whether changes in certain metabolites are linked to sleep loss induced impairments in behavior or changes in brain functioning.

High-density EEG was applied in different contexts and for different purposes in our experimental study. In the next section, general advantages and limitations of this neuroscientific method will be elaborated and the distinct assessments performed will be discussed with a focus on aspects arising due to conditions of increased sleep pressure.

5.1.2 High-density electroencephalography recordings

The method of EEG allows the non-invasive recording of neuronal activity with high temporal resolution (Jäncke, Heuer, Rösler, & Tack, 2005). Such a high temporal resolution allows the assessment of fast occurring and changing brain processes, e.g., oscillating neural activity at different frequencies (M. X. Cohen, 2014). It is a relatively inexpensive and rather mobile method, what makes it readily accessible to many researchers and environments. The standard EEG, consisting of only a few electrodes recording neuronal activity at some distinct sites over the cortex, has, however, a poor spatial resolution (Gevins, Leong, Smith, Le, & Du, 1995). This poses a major constraint of the method when local rather than global brain processes are of interest. This constraint can be overcome by applying high-density EEG, i.e., by markedly increasing the number of electrodes distributed over the cortex (Gevins et al., 1995).

The increased number and density of electrodes also introduces potential problems. For example, electrode bridging and electrolyte spreading may occur, which can result in a smaller signal to noise ratio compared to standard EEG (Greischar et al., 2004). Furthermore, volume conductance blurs the EEG topography (Gevins et al., 1994; Gevins et al., 1995). Another potential problem in high-density EEG topographies is the inverse solution problem (Wendel et al., 2009). The measured electrical activity at the scalp surface represents a sum of ongoing neural activity in the brain. Many different combinations of ongoing activity in the brain can result in the same pattern measured at the scalp surface. Thus, it can be difficult to determine the true origin of electrical activity measured in the scalp EEG. In high-density EEG measurements, this can be overcome by applying procedures of source localization (Wendel et al., 2009), e.g., standardized low resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002). However, in terms of

sleep SWA it has been shown, that the findings from analyses of EEG topographies are very similar and revealed effects in the same cortical regions as source localization procedures (Murphy et al., 2011).

EEG is the gold-standard method to assess sleep (Iber et al., 2012). In the past, the importance of local aspects of sleep became increasingly evident (Lustenberger & Huber, 2012). Even though the spatial resolution of high-density EEG is not as excellent as for example in functional magnetic resonance imaging (fMRI; Gevins et al., 1995), the combination of high temporal and spatial resolution of high-density EEG allows the mapping of distinct oscillating patterns across the cortex (M. X. Cohen, 2014). Consequently, power distribution maps of specific frequency domains can be generated. During sleep for example, SWA/SWE is a marker for sleep pressure and the restorative aspect of sleep (cf. section 3.2.2) and the topography of SWA/SWE may reveal information on local differences in sleep pressure regulation (cf. Lustenberger & Huber, 2012). Power maps, i.e., topographies of spectral power measures, can also reveal information on local aspects of sleepiness during wakefulness. Spectral power in the theta frequency range (5-9 Hz), i.e., theta activity during resting wakefulness has been shown to track increases in homeostatic sleep pressure (Aeschbach et al., 1997; Cajochen et al., 1995; Finelli, Baumann, Borbely, & Achermann, 2000). Furthermore, the increase in theta activity during wakefulness occurs in a use-dependent way and is locally related to the increase in SWA during subsequent sleep (Hung et al., 2013). Thus, future analysis with regard to theta activity topographies in our data set may give additional insights into local build-up dynamics of sleep pressure and their relationships to behavioral impairments during the course of a day in chronic SR.

Beside the assessment of spontaneous brain oscillations (e.g., during sleep or resting wakefulness) as described above, it is also possible to record the neuronal response to a defined event by EEG. A typical measure obtained during task execution for example, is the event-related potential (ERP; Picton et al., 2000). The averaged neural response over several trials of a task results in increased signal to noise ratio, as the averaging process mostly removes random background activity (Dawson, 1951; Mouraux & Iannetti, 2008). However, systematic noise may confound ERP measures. Sources for systematic noise may be eye movements in response to the occurrence of a stimulus for example (Picton et al., 2000). Therefore, further data cleaning may be necessary (e.g., independent component analysis, ICA; Jung et al., 2000). A further problem - especially with regard to the assessment of sleep loss induced effects - is that ERPs depend on the degree to which a subject is willing or able to engage in the task, or in other words, pays attention to the stimulus (Picton et al., 2000). This prerequisite may be compromised under conditions of high

sleep pressure, as attentional, sensory processing and motivational deficits may occur due to increased sleep pressure (Goel et al., 2009).

TMS allows the non-invasive, direct stimulation of specific brain regions by the principle of electromagnetic induction (Rosanova et al., 2012). In combination with high-density EEG (TMS-EEG) one can measure the evoked electrical response and determine local cortical excitability and the propagation and distribution of the induced activation, i.e., the effective connectivity within a network (Rosanova et al., 2012). When applied in combination with a stereotactic neuro-navigation system, the evoked responses are highly reproducible (Casarotto et al., 2010; Lioumis, Kicic, Savolainen, Makela, & Kahkonen, 2008). In contrast to methods based solely on the temporal correlation of activity in distinct brain areas (e.g., EEG coherence analysis; Hesse, Moller, Arnold, & Schack, 2003), the perturbational approach of TMS-EEG allows the assessment of causality of cortical interactions (Paus, 2005). Moreover, due to the direct stimulation, it does not rely on the subject's motivation or ability to engage in a task and bypasses sensory and motor pathways (Rosanova et al., 2012). This makes this method especially interesting for investigating brain functioning under high levels of sleep pressure, as a subject's abilities to perform may be impaired (Goel et al., 2009).

Despite the clear advantages TMS-EEG has to offer, there are some methodological issues which need to be considered in the interpretation of TMS-EEG data. Namely, the TMS pulse not only induces magnetic artifacts in the EEG signal but can also directly activate facial and cranial muscles (Rosanova et al., 2012; Siebner et al., 2009). The magnetic artifact is restricted to about the first 8 milliseconds with TMS-compatible amplifiers and electrodes (as used in our recordings; Veniero, Bortoletto, & Miniussi, 2009), thus, not causing long-lasting effects for the EEG signal. In contrast, the muscle activation on the one hand contaminates large parts of the initial evoked response (Rosanova et al., 2012; Siebner et al., 2009) and on the other hand can also lead to a decay artifact resulting from movement of the electrodes (Rogasch et al., 2014; Virtanen, Ruohonen, Naatanen, & Ilmoniemi, 1999) which can even last longer, i.e., for hundreds of milliseconds. Therefore, careful inspection of the data is required and there frequently is a need to further clean the data from residual artifacts (Rogasch et al., 2014). There are several procedures which can be applied, as for example the removal of artifacts by template subtraction (e.g., Bender et al., 2005; Thut, Ives, Kampmann, Pastor, & Pascual-Leone, 2005), ICA (e.g., Korhonen et al., 2011; Rogasch et al., 2014) or principal component analysis (PCA; e.g., Litvak et al., 2007; Maki & Ilmoniemi, 2011). However, all of these procedures also induce the possibility of changing or removing physiologically meaningful signal (e.g., Li & Principe, 2006), thus, complicating the analyses and the interpretation of results even more.

5.1.3 Clinical study design

In our clinical study, we prospectively assessed sleep-wake disturbances in TBI patients six and 18 months after the TBI event. We compared the assessed measures to the ones obtained from a healthy control group without history of TBI. This control group was carefully matched for age and gender. However, chronically insufficient sleep durations are highly prevalent in society (Groeger et al., 2004; Liu et al., 2016; Tinguely et al., 2014). This may be a potential confounder in such group comparisons, if such individuals are not included in the control group but are eligible to be included in case they are TBI patients. Thus, we additionally matched the control group to the patient group in terms of sleep satiation. More precisely, we matched the groups in terms of the difference between sleep durations on working days to sleep durations on weekends. This difference is indicative of insufficient sleep obtained during working days, which is in turn compensated on weekends. With this procedure we aimed at minimizing the possibility that differences between groups were merely a result of behaviorally induced insufficient sleep durations. Furthermore, we accepted control subjects which showed marginally increased sleep-apnea indices and objective sleepiness measures. This decision was again based on the finding that marginally elevated levels are common in the population (Mignot et al., 2006). Thus, excluding such individuals from the control group would have resulted in an artificial rather than representative control sample. In an ideal study design, subjects from both groups should be given extended bed times for several consecutive days prior to the assessment of increased sleep need and excessive daytime sleepiness. By these means, it could be definitely ruled out, that differences in prior sleep-wake history drive differences between groups. Furthermore, this procedure would allow determining the individual sleep need (c.f. section 3.3.2). Additionally, one could assess whether excessive daytime sleepiness persists despite achieved sleep satiation. However, adding an extensive sleep extension to such a protocol may pose a large challenge for the feasibility of study conductance, especially in a clinical context.

5.2 Comparability of effects and correlates of increased sleep pressure following acute SD and chronic SR

5.2.1 Sleep EEG correlates and behavioral effects of acutely and chronically increased sleep pressure

In our within-subject design study, we found that the initial SWA increase, i.e., at the beginning of sleep, following acute SD and chronic SR was highly correlated across the two conditions. Furthermore, the increase in SWA was related to the impairments in vigilance across both conditions. This indicates that the individual homeostatic increase in sleep pressure is qualitatively comparable in acute and chronic sleep loss. Quantitatively, both the increase in SWA and the impairments in vigilance were stronger following acute SD compared to chronic SR, suggesting that homeostatic sleep pressure was more increased after 40 hours of acute SD than after seven nights of chronic SR with five hours of sleep opportunity per night in our healthy, young, male subjects.

For the comparison of SWA increase after acute SD and chronic SR we only included the first night following all seven nights of chronic SR but not the chronic SR nights *per se*. Investigating these nights would allow to assess the time course of SWA increase during chronic SR. In other words, one could assess whether there is a gradual increase over all nights with restricted sleep and whether there is a dose-response. While there seems to be at least no major qualitative difference between the increases observed in initial SWA after acute SD and chronic SR, the time course might be different as it is assumed for neurobehavioral impairments (McCauley et al., 2009).

Neurobehavioral impairments are related to the increase in homeostatic sleep pressure resulting from sleep loss. Additionally, the extent of impairments is influenced by a circadian process, resulting in fluctuating levels of impairments across 24 hours during acute SD (Lim & Dinges, 2008). In our laboratory study, we controlled the circadian fluctuations by averaging behavioral performance across multiple test sessions per day which all were completed at the same times of the day across conditions. Such a procedure may reduce the influence of circadian fluctuations on the results. However, it does not allow drawing any conclusions about the interaction between homeostatic sleep pressure and the circadian influence (Van Dongen, Bender, & Dinges, 2012).

The prediction of individual basic neurobehavioral performance deficits following sleep loss has been shown to improve significantly, when not only including inter-individual differences in the sleep homeostatic process into the model but also considering inter-individual differences in the circadian influence (Van Dongen et al., 2012). Consequently, accounting for circadian process differences may also explain some additional variance in the association between initial SWA

increase and impairments in vigilance. Furthermore, chronic SR can induce a shift of the circadian rhythm (Lo et al., 2012). This poses a potential bias when comparing test sessions completed at the same time of day, as the circadian time would be shifted relative to the time of day. The circadian rhythm shift is expected to be rather small when sleep durations are curtailed at both ends of the night in chronic SR (Lo et al., 2012), as realized in our study. Nevertheless, obtaining a circadian rhythm profile during chronic SR may help to quantify such a potential bias. Additionally, given that test sessions are conducted frequently enough, measures to be compared may also be realigned to the circadian phase individually for every condition (cf. Lo et al., 2012).

In contrast to the SWA increase and vigilance measures, risk-preference was only significantly different from after regular sleep following chronic SR but not following acute SD. This divergent finding seems to contradict the assumption that the effects of acute SD and chronic SR are qualitatively comparable but only differ in magnitude depending on the extent of additionally induced sleep pressure. In that case, a dose-response effect on risk-taking behavior - which is in accordance with the increase in sleep pressure indexed by electrophysiological correlates and vigilance impairments - would have been expected. As discussed above, vigilance was strongly impaired after acute SD and only moderately (non-significantly) after chronic SR. Thus, one possible explanation is that vigilance was too impaired for task execution after acute SD while it was still preserved enough after chronic SR to execute the task. It has been noticed before that impairments in basic neurobehavioral functioning might underlie impairments seen in higher-order cognitive functions (Lim & Dinges, 2010; Lo et al., 2012). In our case, one could speculate that the impairments in basic neurobehavioral functioning after acute SD may have masked changes in risk-preference occurring as a result of increased sleep pressure. Indeed, the number of trials in the risk-task without a response was highest in the condition of acute SD and lower after chronic SR. This may suggest an inability for proper engagement in task execution after acute SD. Nevertheless, if subjects did not show a change in risk-preference because they were unable to maintain vigilant attention during the task, a change of risk-preference should be evident in those subjects who did not show a noticeable increase in lapses of vigilance after acute SD. However, lapses in vigilance and the change in risk-preference were not significantly associated in either condition. Thus, it seems unlikely that differences in vigilant attention during task execution were the sole or the main reason for the divergent finding between acute SD and chronic SR in terms of changed risk-preference.

An alternative or additional explanation may be that decision-making network properties gradually change with increasing sleep pressure. This may eventually lead to a break-down of function when sleep pressure exceeds a certain level. Thus, one can speculate that a moderate

increase in sleep pressure may change the risk-preference towards a higher drive for risky decisions while too much sleep pressure may lead to a break-down of proper decision-making, i.e., to a failure to implement the individual risk-preference in the choices made. Accordingly, we and others found that acute SD primarily affects choice consistency (Menz et al., 2012), i.e., the implementation of risk-preference *per se*, which was only moderately affected after chronic SR. Thus, changes in risk-preference would not be evident after acute SD due to a failure of their implementation. In line with this explanation, it has been proposed that acute SD and severe chronic SR (less than 4 hours of sleep opportunity per night) result in progressively escalating performance impairments while in less severe chronic SR performance impairments accumulate more gradually (McCauley et al., 2009).

Taken together, our findings indicate that there may be a gradual impairment in performance in response to increased sleep pressure, up to a certain level, when a break-down of functioning occurs. However, despite the large amount of evidence for behavioral impairments occurring as a result of increased sleep pressure, the exact underlying mechanisms of sleep loss induced function deterioration remain largely unknown. Advanced neuroscientific methods may yield insights into these mechanisms beyond of what the assessment of changes in behavior can provide.

5.2.2 Investigation of cortical excitability and network property changes after sleep loss

To further investigate whether a break-down of function occurs in decision-making after acute SD but not after chronic SR, we assessed the responsiveness of cortical areas involved in decision-making and decision-making network functioning. Investigating the functional engagement of a given cortical area or the respective network properties during task execution may be confounded by a potential reduction in task engagement, impaired vigilance or altered sensory processing, especially after acute SD (for review see Goel et al., 2009).

TMS-EEG does not rely on the subject's motivation or ability to engage in a task and bypasses sensory and motor pathways (Rosanova et al., 2012). Thus, it provides an interesting tool to assess decision-making network functioning, especially in the context of sleep loss. In an exploratory approach, we applied single-pulse TMS to the right prefrontal cortex in eight of our subjects to assess local cortical excitability on the one hand and the globally induced activation on the other hand in a preliminary analysis. Previously, the right prefrontal cortex, especially the dorsolateral prefrontal cortex, has been linked to risk-taking behavior (e.g., Ernst et al., 2002; Fecteau et al., 2007; Gianotti et al., 2009; Knoch et al., 2006). Furthermore, in our study, we have found that low sleep intensity (as reflected by low SWE) in the right prefrontal cortex and a decrease in stimulus-evoked activity in the same area during the choice process were linked to an increase in risk-

seeking after chronic SR. Thus, the right dorsolateral prefrontal cortex was chosen as the stimulation spot. The exact location was determined based on the individual's structural magnetic resonance images (MRI). A neuro-navigation system was used for precise and reproducible targeting. Local cortical excitability has previously been shown to increase as a function of wakefulness and to decrease as a function of sleep (Huber et al., 2013). It thus closely follows the time course of SWA and therefore mirrors the accumulation and dissipation of sleep pressure.

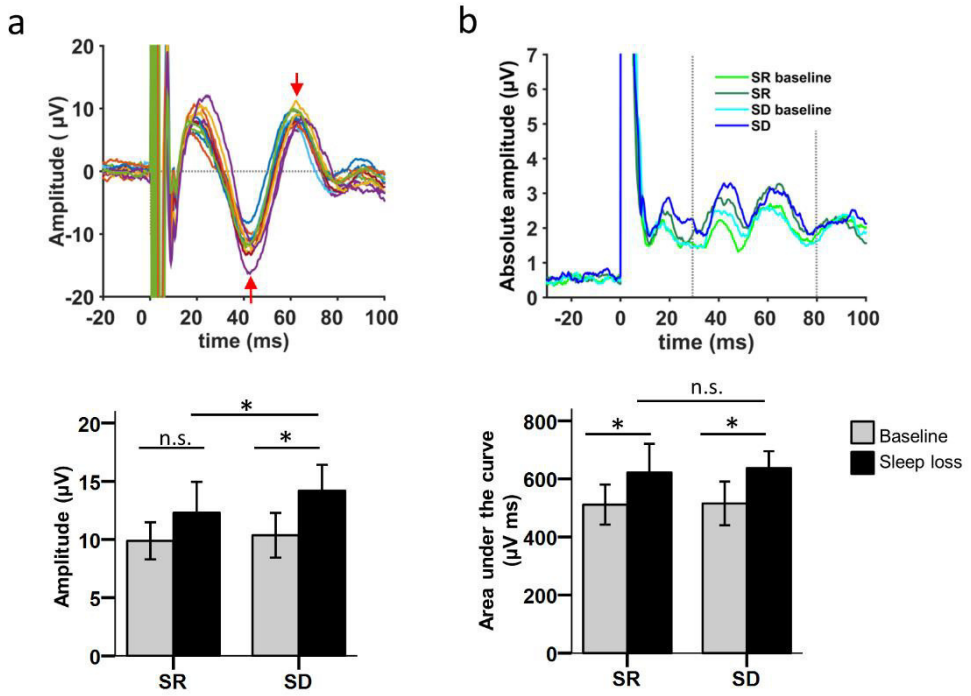

Figure 4 – Transcranial magnetic stimulation (TMS) evoked activity recorded by simultaneous electroencephalography (EEG). Zero corresponds to the time point of the TMS pulse. (a) The evoked response (top: shown for all assessments in one subject) was recorded in one electrode close to the stimulation site to assess local cortical excitablity changes. The peak-to-peak amplitude between the first artifact-free negative to positive deflection was calculated (red arrows) in the afternoon after acute sleep deprivation (SD), following chronic sleep restriction (SR) and prior to both sleep loss conditions (baseline; BL) and compared by paired samples T-tests. (b) To asses the globally induced activation we calculated the area under the curve (AUC) of the absolut signal in a selection of globally distributed electrodes not showing major stimulation induced artifacts (top: absolute evoked signal averaged over all subjects). The time-window for AUC assessment was set at 30 to 80 ms after the TMS pulse. Mean AUC values across all assessed electrodes were compared by paired samples T-tests. *P < 0.05. n.s.: P > 0.05.

In this preliminary and explorative analysis we found that, relative to baseline, local cortical excitability in the right prefrontal cortex was significantly increased only after acute SD whereas the subtle increase after chronic SR failed to reach significance (Figure 4a). In contrast, the globally evoked activation was increased after acute SD and chronic SR, with the increase not being different between the two conditions (Figure 4b). The change in local cortical excitability is in agreement with the dose-response pattern seen in the SWA increase, the impairment in vigilance and the reduction in choice consistency, i.e., implementation of risk-preference, with the effects being of larger magnitude after acute SD than after chronic SR but pointing into the same direction. In contrast, the comparable increase in globally induced activation in both conditions could reflect a diminished signal propagation following acute SD. More precisely, the locally induced activation in the target region is increased more after acute SD than after chronic SR. Consequently, one would expect that more induced activity in the target area goes along with a stronger increase in the signal that is propagating to distant areas. However, as there is no difference between the increase in globally induced activation after acute SD and chronic SR, this may be interpreted as a proportionally lower signal propagation after acute SD. This could potentially reflect a break-down of network effective connectivity after acute SD. Nevertheless, these analyses are only a preliminary first step and the interpretation remains speculative. More detailed analysis of directed signal propagation is needed to conclude whether there is a network break-down following acute SD and whether changes in signal propagation within the network following chronic SR are associated with the observed increase in risk-seeking. Furthermore, the methodological issues inherent to the method of TMS-EEG require some caution when interpreting TMS-EEG data (cf. section 5.1.2). Especially, since targeting the dorsolateral prefrontal cortex is often resulting in strong cranial muscle activations (Rogasch et al., 2014).

With regard to the main aim of this thesis, the presented findings of both the homeostatic increase in initial SWA and the respective association with impairments in vigilance and of the preliminary findings from the TMS-EEG analysis, i.e., the increase in cortical excitability, provide evidence that the effects observed after acute SD and chronic SR may show quantitative differences but are qualitatively comparable. Further investigations are needed to determine whether more complex behavior, i.e., risk-taking is differently affected due to a break-down of function occurring at high levels of sleepiness. In a next step, the focus will be set on the potential underlying mechanisms of the described effects of chronic SR on behavior.

5.3 Potential underlying mechanisms of behavioral changes following chronic SR

5.3.1 Association between behavioral changes after chronic SR and the sleep EEG

We found that the increase in risk-seeking after chronic SR was related to less SWE in the right prefrontal cortex during the preceding short night. Interestingly, this brain area is known to be involved in controlling risk behavior and inhibiting risky decisions. This has been shown by studies with brain lesion patients (e.g., Clark, Manes, Antoun, Sahakian, & Robbins, 2003) and by non-invasive brain stimulation studies in healthy individuals (Fecteau et al., 2007; Knoch et al., 2006). SWE is thought to reflect the restorative aspect of sleep (Tononi & Cirelli, 2006). Insufficient local restoration during short sleep may impair daytime functioning of this particular area and may, thus, be a potential underlying mechanism of the sleep loss induced increase in risk-seeking. It has been shown that the extent of all-night SWA increase during recovery sleep following acute SD is linked to the restoration of inhibitory performance, which was further accompanied by a subsequent increase in right prefrontal cortex activity during task performance (Mander et al., 2010). Along the same line, the local amount of SWE during the short nights may be an indicator for how well a function relying on the respective brain area is preserved, i.e., stays close to baseline performance even if sleep is restricted.

An alternative explanation for the observed association between locally low SWE and the increase in risk-seeking may be discussed based on the fact that local SWA (and thus also SWE) is influenced by the use of the corresponding brain area during preceding wakefulness (Goel et al., 2014; Huber et al., 2006; Huber et al., 2004; Hung et al., 2013; Kattler et al., 1994). More precisely, the increased use of a given cortical area during wakefulness leads to a local increase in SWA in this area during subsequent sleep (Huber et al., 2004; Kattler et al., 1994). Such an increase may also occur on top of a global increase of SWA due to prolonged wakefulness (Goel et al., 2014; Hung et al., 2013). In turn, deprivation of activity in a given cortical area during wakefulness leads to a local decrease of SWA in this area (Huber et al., 2006). Accordingly, reduced engagement of the right prefrontal cortex in cognitive processes (e.g., decision-making) during wakefulness may be reflected by less use-dependent local SWE during subsequent sleep. Due to the correlational approach of our study, we cannot conclude whether low local SWE values in the first place (i.e., insufficient sleep-dependent restoration during chronic SR) caused reduced right prefrontal cortex functioning or if reduced right prefrontal cortex functioning was caused in the first place by other effects of chronic SR (e.g., insufficient recruitment for task performance by other brain areas) and was consequently just reflected in low local SWE values. Future studies, applying for example brain stimulation methods, may help to draw causal conclusions on the association between low local SWE during chronic SR and the observed

changes in behavior. For example, by increasing SWE in the right prefrontal cortex during chronic SR, the increase in risk-seeking following chronic SR should be prevented or diminished if insufficient restoration of this brain area is causing the increase in risk-seeking.

5.3.2 Potential network changes due to increased sleep pressure

Impaired functioning of a given brain area, regardless of whether it is caused or whether it is reflected by low levels of SWE, could lead to a change of network functioning or to a change of balance within a network of brain regions which are involved in a cognitive process. The right prefrontal cortex, especially the dorsolateral part, is associated with cognitive self-control in the context of risk (Knoch & Fehr, 2007) and is thought to inhibit prepotent urges (Hare, Camerer, & Rangel, 2009). It has been shown that the activation of reward regions in the brain in response to risky choices is increased following acute SD (Venkatraman et al., 2007). The reduced engagement of the right prefrontal cortex could then be insufficient to counteract this increase, resulting in the apparent behavioral consequences. Furthermore, it has been shown that acute SD leads to an increased drive for high gains (Venkatraman et al., 2011). Accordingly, in our and other risk tasks the risky option is usually associated with higher potential gains (cf. Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006). The lack of or the proportionally reduced inhibitory influence of the right prefrontal cortex could make the subjects choose the risky option due to the potential high gains. Indeed, there is evidence that a weaker top-down inhibitory control from the right prefrontal cortex to reward-oriented brain regions is associated with higher risk-seeking (Lee & Jeong, 2013). In addition, the finding that lower whole-brain connectivity of the right dorsolateral prefrontal cortex is associated with higher risk-seeking (Weber, Messing, Rao, Detre, & Thompson-Schill, 2014) is supportive of the assumption that a reduction in the inhibitory influence of the right prefrontal cortex during chronic SR may lead to the observed increase in risk-seeking.

5.3.3 Gradual amplification of behavioral changes during chronic SR?

SWA has been shown to increase and decrease in a use-dependent manner (Goel et al., 2014; Huber et al., 2006; Huber et al., 2004; Hung et al., 2013; Kattler et al., 1994). Thus, assuming that insufficient restoration during sleep leads to impaired or reduced engagement of a brain area during consecutive wakefulness, this potentially results in a reinforcing feedback loop, causing a gradual increase of the impairment: A local insufficient restoration of inhibitory brain regions (e.g., right prefrontal cortex) may cause other brain regions to show increased activity due to a lack of the inhibitory influence (e.g., reward system). As a result, the latter may display an even

more pronounced increase in SWA (thus also SWE) the following night (due to the use-dependent increase in SWA). This increase would be particularly pronounced relative to those brain areas which showed less activation (e.g., right prefrontal cortex) and thus also a proportionally lower increase in local SWA/SWE during subsequent sleep. This, in turn, may lead to a further increase of the imbalance in the network the next day, which then again leads to a higher relative difference in SWA/SWE during subsequent sleep between the inhibitory regions and the regions with increased activity. A gradual increase in risk-seeking during the course of chronic SR would be the consequence.

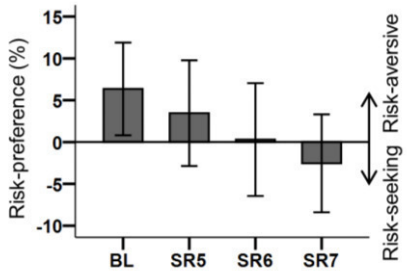

Figure 4 – Gradual change of risk-preference across the evenings following the last chronic sleep restriction (SR) nights (SR5, SR6, SR7) compared to regular sleep. Repeated-measures analysis of variance revealed a significant change ($F(1.997, 25.965) = 3.552$, $P = 0.043$, Huynh-Feldt correction of degrees of freedom). The polynomial contrast revealed a significant linear trend in the data ($F(1, 13) = 9.004$, $P = 0.010$).

In our comparisons regarding risk-preference, we focused on the change observed after the full seven nights of chronic SR. However, we also assessed risk-taking behavior during the preceding two evenings. Comparing the measures of risk-preference obtained in the evenings following the fifth, sixth and seventh night of SR to the evening after regular sleep, indeed, revealed a significant linear increase in risk-seeking (Figure 5). However, to further investigate the possibility of impairment reinforcement by the above-discussed mechanism, one would need to not only record behavioral data during the whole course of chronic SR but also to assess SWE

during every SR night. If, indeed, such reinforcement occurs, one would expect a gradual change of local SWE values and an association with the gradual change in behavior.

5.3.4 Potential underlying mechanism of individual differences in sleep loss induced behavioral changes

EEG slow waves result from cortical neurons which synchronously undergo slow oscillations (< 1 Hz) in membrane potential (e.g., Amzica & Steriade, 1998). These oscillations are characterized by depolarized up-states on the one hand, during which neurons show sustained firing, and on the other hand by hyperpolarized down-states, referring to neuronal silence (e.g., Steriade, Timofeev, & Grenier, 2001). The extent of synchrony among cortical neurons engaging in slow oscillations is influenced by the strength of their synaptic connections and their regional density (Esser et al., 2007; Vyazovskiy et al., 2009). In other words, the stronger and more densely the neurons are inter-connected, the more synchronous they engage in the slow oscillations. Higher synchrony in turn is reflected in higher amplitudes of EEG slow waves and, thus, also in higher SWA/SWE (Esser et al., 2007; Vyazovskiy et al., 2009). Thus, the SWA/SWE topography may indicate how well-connected distinct brain areas are. The individual topography, despite being slightly altered by sleep loss, is highly stable across several measurements. It is, therefore, thought to reflect stable functional anatomical differences between individuals (Finelli, Achermann, et al., 2001).

Sleep loss-induced impairments are thought to reflect the failure of function due to the emerging local restoration need which results from the repetitive use of neuronal assemblies involved in a given cognitive task (Van Dongen, Belenky, et al., 2011). Individual differences in the vulnerability to sleep loss induced cognitive impairments are thought to result from differences in the susceptibility to such an induced fatigue effect in distinct neuronal assemblies (Van Dongen, 2012). Accordingly, differences in SWA/SWE topography could indicate such individual differences in vulnerability across distinct cognitive domains: The less well-connected a given neuronal group is, the more vulnerable it may be to functional deterioration when extensively used.

As the topographies are rather stable within an individual, also baseline measures could predict how vulnerable a given brain region is to function deterioration due to the challenge of sleep loss. Along these lines, functional MRI (fMRI) studies reported that differences in connectivity measures during baseline may be predictive for the extent of cognitive impairments due to acute SD (e.g., Yeo, Tandi, & Chee, 2015). Accordingly, we also found a trend that baseline SWE values are associated with the increase in risk-seeking after chronic SR in the electrodes in which the SWE values during chronic SR were significantly associated with the change in risk-seeking

(r (13) = -0.48, P = 0.08; Pearson correlation coefficient; two-sided permutation testing). Thus, lower local SWE values may indicate a higher vulnerability to fatigue effects in distinct neuronal assemblies. In a next step, one could test this hypothesis by non-invasive brain stimulation, e.g., by repetitive TMS (rTMS). Namely, function disruption of a given brain area should be more effective in individuals displaying locally low SWE values than in individuals with high values.

Taken together, our findings indicate that chronic SR may alter the activity of particular brain regions, leading to a change in associated behavior. Potentially, this is the result of the altered relative contributions of inhibiting and driving brain areas in the respective brain network. We assumed that insufficient local restoration in the right prefrontal cortex during chronic SR may cause the observed increase in risk-seeking. This could be further assessed by locally increasing SWE in this brain region during chronic SR, which should in turn prevent or diminish the increase in risk-seeking following chronic SR. Such a local stimulation would, indeed, be necessary if assuming that the underlying mechanism of increased risk-seeking after chronic SR is a diminished relative influence of the right prefrontal cortex within the network. Hence, increasing SWE globally would also further strengthen the influence of brain regions already having an enhanced impact on decision-making. Consequently, no prevention of increased risk-seeking could be expected.

So far, the findings of this thesis provided evidence for far-reaching consequences of chronic SR on behavior and potential underlying mechanisms in a healthy, young population. As different clinical conditions are associated with sleep-wake disturbances, in the next section, chronically increased sleep pressure and potential effects on behavior in clinical contexts will, thus, be discussed.

5.4 Chronically increased sleep pressure in the clinical context

5.4.1 Awareness of chronically increased sleep pressure

ISS is a condition, in which clinically relevant symptoms of excessive sleepiness arise in the absence of a physiological cause but rather because of the chronic restriction of sleep durations below the individual need (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014). In our study in healthy subjects, we found that chronic SR itself leads to an overestimation of sleep continuity and a marginal overestimation of total sleep time during SR. The same direction of change was seen for recovery sleep following acute SD but to a lesser extent. Thus, high sleep pressure, especially in combination with short sleep durations, may change sleep perception. This, in turn, could explain why individuals diagnosed with ISS often do not notice that their sleep duration is insufficient and that this, consequently, causes the symptoms which urge them to consult a sleep disorders clinic (*American Academy of Sleep Medicine. International classification of sleep disorders*, 2014; Komada et al., 2008). The underestimation of sleep insufficiency is in line with the finding that individuals underestimate subjective sleepiness arising during chronic SR (Philip et al., 2012; Van Dongen, Maislin, et al., 2003) and that subjects in our study did not notice their increased drive for risk in our study.

Similarly, TBI patients in our clinical study underestimated the extent of their excessive daytime sleepiness and their increased sleep need. Thus, it seems that in both healthy and some diseased conditions, chronically increased sleep pressure is subjectively not well perceived. Interestingly, healthy subjects have been shown to be more aware of their gradually increasing sleepiness during acute SD than chronic SR (Van Dongen, Maislin, et al., 2003). This, again, is in line with our finding that acute SD introduces a less strong misperception of sleep duration and continuity than chronic SR. Thus, it seems plausible that chronic SR impacts self-evaluation more strongly than does acute SD. A possible explanation is that individuals subjectively get used to the feeling of the chronically increased sleep pressure and, thus, become less sensitive in noticing the discrepancy to normal or baseline levels of sleepiness.

5.4.2 Signs of chronically increased sleep pressure in traumatic brain injury

In our clinical study of TBI patients, we found that TBI is associated with a higher sleep need (as indicated by more sleep per 24 hours) and objective daytime sleepiness. Furthermore, six months after the TBI event we also found signs of increased sleep pressure in terms of more consolidated sleep and a trend for higher levels of SWA. Thus, the daytime sleepiness could be the result of chronically increased sleep pressure due to an unmet increased sleep need. Nevertheless, the exact causes of increased sleep need remain unknown. On the one hand, acute neuronal recovery

processes after TBI could necessitate increased deep sleep (Tononi & Cirelli, 2006). In favor of this hypothesis is the finding that the increased sleep need was related to TBI severity. On the other hand, it is certainly possible that persisting impairments of wake promoting neuronal populations arise due to the TBI event, which may chronically increase the urge to sleep in these patients. This assumption is corroborated by the findings of reduced numbers of wake-promoting hypocretin, histamine, and monoaminergic brainstem neurons after fatal TBI (Baumann et al., 2009; Valko et al., 2015).

According to the two-process model of sleep regulation, the propensity of sleep initiation is determined by the interaction between the homeostatic sleep pressure and the threshold of sleep onset (Borbély, Achermann, Trachsel, & Tobler, 1989). The latter is influenced by the circadian process and, thus, may reduce sleep propensity despite high levels of homeostatic sleep pressure or in turn increase sleep propensity despite relatively low levels of homeostatic sleep pressure. Assuming that increased sleep durations and excessive daytime sleepiness six months after the TBI event were solely or mainly caused by insufficient wake-promotion, this would result in increased sleep propensity due to a lower threshold of sleep onset in absence of increased homeostatic sleep pressure. As a result, we would not expect more consolidated sleep itself or higher SWA levels, which in turn reflect homeostatic sleep pressure. We did, however, find the opposite, namely an increased consolidation of sleep and a trend for higher SWA six months after TBI compared to matched controls.

However, SWA and consolidation of sleep were not significantly different from controls anymore 18 months after the TBI event. In contrast, daytime sleepiness and higher sleep need per 24 hours persisted but were not related to TBI severity (anymore in the case of sleep need). Thus, on the one hand we may speculate that in the more acute phase, i.e., six months after the event, sleep need may be increased merely - albeit not necessarily only - due to acute recovery processes, which may eventually result in daytime sleepiness when this higher sleep need is not met. On the other hand, in a long run, i.e., 18 months after the event, persisting damage to the arousal-promoting systems may cause the chronically increased sleep need and excessive daytime sleepiness. Future studies investigating sleepiness and sleep in TBI patients even sooner after the event and studies applying more detailed neuroanatomical methods to assess micro-lesions in the brainstem of surviving patients, e.g., MRI-based methods, may provide further insights into the underlying nature of increased sleep need and sleepiness in TBI.

5.4.3 Implications of the link between chronically increased sleep pressure and increased risk-seeking in a clinical context

Our finding that chronic SR increases risk-seeking may also have clinical implications: ISS and other clinical conditions which are accompanied by a chronically unmet sleep need may be associated with increased risk-seeking. We found that this increase only occurs after chronic SR but not after acute SD. This divergence was interpreted as the result of increased sleep pressure leading to an increase in risk-seeking up to the level of sleepiness that disables an individual to implement the subjective risk-preference in its choices altogether (i.e., as is the case after acute SD, see section 5.2.1). Thus, the patients with the highest levels of excessive daytime sleepiness may not be the ones who are most prone to increased risk-seeking behavior. Instead, those with moderately increased sleep pressure may be most susceptible to such an increase. Accordingly, the increase in risk-seeking was not associated with subjective excessive daytime sleepiness or impairments in objective vigilance in our study.

Even though in our study we assessed risk-taking behavior only in a financial context, the increased risk-seeking behavior may also occur in other occasions. For example, it has been shown that excessive fast driving is associated with low right lateral prefrontal activity (Jäncke, Brunner, & Esslen, 2008). Interestingly, we observed that low SWE during SR in this brain region is related to the increase in financial risk-seeking induced by chronic SR. Consequently, if chronic SR impacts functioning of the right (lateral) prefrontal cortex, this could have an impact also on the assessment of driving abilities. Up to date, the main focus regarding the effect of sleepiness on driving performance lies on vigilance and maintenance of wakefulness (Fromm, 2008). The possibility that insufficient sleep may also lead to riskier driving may be a new aspect to be considered. Also, the individual risk-preference has been shown to be distinct across different contexts (Pennings & Smidts, 2000). It, therefore, remains to be investigated whether chronic sleep loss can induce changes in risk-taking in contexts other than financial decision-making and whether the susceptibility to changes in risk-preference induced by chronic sleep loss varies across different contexts within an individual.

TBI itself has previously been associated with increased risk-seeking behavior (e.g., Sigurdardottir, Jerstad, Andelic, Roe, & Schanke, 2010; Visser-Keizer, Westerhof-Evers, Gerritsen, van der Naalt, & Spikman, 2016). TBI often impacts frontal areas (Wallesch et al., 2001). Such damage, in turn, could diminish the inhibitory control in risk-taking behavior (Glascher et al., 2012). Our findings that TBI seems to be associated with an unmet increased sleep need and that chronically increased sleep pressure may induce increased risk-seeking behavior provides a new potential underlying mechanism of increased risk-seeking behavior after TBI. In other words, increased risk-seeking in TBI patients could also or additionally be caused

by chronically insufficient sleep rather than by brain damage per se. Potentially, these mechanisms occur in parallel and may even potentiate. Such a link between chronically insufficient sleep and increased risk-seeking behavior may also apply to other clinical conditions in which high risk-seeking behavior has been reported. For example, obesity has previously been associated with aberrant decision-making behavior (Davis, Levitan, Muglia, Bewell, & Kennedy, 2004; Pignatti et al., 2006). Considering that obesity poses a risk factor for sleep apnea (Kales, Vela-Bueno, & Kales, 1987; Strohl & Redline, 1996), a reduction in total sleep time due to sleep apnea may result in a chronically insufficient sleep and, in turn, may alter risk-taking behavior. A similar link is also plausible in other clinical conditions such as Parkinson's disease, a condition associated with disturbed sleep on the one hand (e.g., Wienecke et al., 2012) and with (medication induced) increased risk-taking behavior and impulsivity on the other hand (Djamshidian et al., 2010). Hence, chronically insufficient sleep may potentiate these effects. However, whether also chronically disturbed and disrupted sleep increases risk-seeking or whether only a chronic curtailment of undisturbed sleep as in chronic SR in healthy individuals (including ISS) and potentially TBI, remains to be clarified.

Sleep loss induced impairments in vigilance have been shown to be rather independent from the level of baseline performance (Frey et al., 2004). Accordingly, the increase in risk-seeking following chronic SR did not depend on the baseline level of risk-seeking in our study. Thus, individuals with pronounced risk-seeking already at baseline may show a further increase due to chronic SR. This indicates that chronic SR may have more detrimental consequences in populations which are, per se, associated with high risk-seeking behavior, for example in pathological gambling (Hollander, Buchalter, & DeCaria, 2000).

The basic science findings of this thesis translated into clinical contexts. This may help to understand the impact of chronically insufficient sleep in clinical conditions and the underlying mechanisms.

5.5 Overall conclusions

Our findings support the notion that there is no major qualitative difference in the homeostatic increase in sleep pressure following acute and chronic sleep loss, as is indicated by the strong relationship between increased initial levels of SWA and the association to impairments in vigilance across both conditions. The picture revealed to be more complicated when assessing changes occurring in more complex behavior, i.e., risk-taking. The results suggest that changes may gradually increase with increased sleep pressure but that a break-down of function occurs at one point when sleep pressure is too high for proper task execution, i.e., following acute SD. This assumption should be further investigated, for example by comparing network functioning with TMS-EEG after acute SD and chronic SR.

We provide first evidence that insufficient local restoration in sleep during chronic SR in the right prefrontal cortex may be linked to a change in risk-taking behavior, potentially by a change in its inhibitory contribution within the network involved in decision-making. This correlative link should be further addressed by systematically increasing local restoration in this brain area during chronic SR, thus, eventually proving causality.

Chronic SR itself was found to change the perception of sleep continuity and duration. This matches the general lack of subjective awareness of impairments resulting from chronically increased sleep pressure (Philip et al., 2012; Van Dongen, Maislin, et al., 2003). Furthermore, we found in our prospective study in TBI patients that they subjectively underestimated the extent of their daytime sleepiness and increased sleep need. In parallel, signs of chronically increased sleep pressure were objectively registered. Thus, a higher sleep need following TBI could result in chronically insufficient sleep durations by not meeting the increased sleep need. The finding that chronic SR increases risk seeking and the indices for chronically increased sleep pressure in TBI may provide an additional link that explains the association between TBI and increased risk-seeking which was reported before (Sigurdardottir et al., 2010; Visser-Keizer et al., 2016). Linking the findings from basic science with conditions of disease may, eventually, help to better understand the consequences of disrupted brain functioning for behavior.

Taken together, this thesis contributed to the understanding of the degree to which effects of acute SD may also apply to chronic SR. Furthermore, it provided insights into potential underlying mechanisms of behavioral changes following chronic SR and some implications which may be relevant for clinical contexts. Considering the high prevalence of insufficient sleep durations in modern society and the high number of clinical conditions associated with daytime sleepiness, understanding the effects and mechanisms of brain function alterations induced by chronically increased sleep pressure poses an important topic to be further investigated in the future.

6 References

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8 Publication List

Peer-reviewed Journal Articles

Maric A., Lustenberger C., Werth E., Baumann C.R.*, Poryazova R.*, Huber R.* (in press). *shared last authorship
Intra-individual increase of homeostatic sleep pressure across acute and chronic sleep loss: A high-density EEG study. *Sleep*.

Maric A., Montvai E., Werth E., Storz M., Leemann J., Weissengruber S., Ruff C.C., Huber R.*, Poryazova R.*, Baumann C.R.* (2016). *shared last authorship
Insufficient sleep: Enhanced risk-seeking relates to low local sleep intensity.
Manuscript submitted for publication.

Maric A.*, Bürgi M.*, Werth E., Baumann C.R., Poryazova R. (2016).
***shared first authorship**
The impact of sleep restriction and sleep deprivation on subjectively perceived and actigraphically derived sleep parameters. Manuscript submitted for publication.

Büchele F., Hackius M., Schreglmann S.R., Omlor W., Werth E., **Maric A.**, Imbach L.L., Hägele-Link S., Waldvogel D., Baumann Christian R. (2016).
Sodium oxybate for excessive daytime sleepiness and sleep disturbance in Parkinson's disease: A double-blind, placebo-controlled, crossover, phase 2a study. Manuscript submitted for publication.

Imbach L.L., Büchele F., Valko P.O., Li T., **Maric A.**, Stover J.F., Bassetti C.L., Mica L., Werth E., Baumann C.R. (2016).
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Imbach L.L., Valko P.O., Li T., **Maric A.**, Symeonidou E.-R., Stover J.F., Bassetti C.L., Mica L., Werth E., Baumann C.R. (2015).
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Kessler T.M., **Maric A.**, Mordasini L., Wöllner J., Pannek J., Mehnert U., van Kerrebroeck P.E., Bachmann L.M. (2014).
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Neurourology and Urodynamics 33:1240–1246.

Lustenberger C.*, **Maric A.***, Dürr R., Achermann P., Huber R. (2012).
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Triangular Relationship between Sleep Spindle Activity, General Cognitive Ability and the Efficiency of Declarative Learning.
PLoS ONE 7(11): e49561.

Conference Contributions and Further Scientific Work

Maric A., Montvai E., Werth E., Storz, M., Leemann J., Weissengruber S., Ruff C.C., Huber R.*, Poryazova R.*, Baumann C.R.* (2016). *shared last authorship

Chronic sleep restriction increases risk-seeking.

Annual meeting of the Children's Research Center, University Children's Hospital Zurich, Switzerland.

Oral presentation.

Maric A., Montvai E., Werth E., Storz, M., Leemann J., Sennrich V., Weissengruber S., Ruff C.C., Huber R.*, Poryazova R.*, Baumann C.R.* (2016). *shared last authorship

Chronic sleep restriction increases risk-seeking.

23rd Congress of the European Sleep Research Society (ESRS) in Bologna, Italy.

Poster presentation.

Maric A., Lustenberger C., Werth E., Sennrich V., Leemann J., Weissengruber S., Ruff C.C., Poryazova R.*, Baumann C.R.*, Huber R.* (2016). *shared last authorship

Sleep EEG correlates of increased risk-seeking during chronic sleep restriction.

Joint Annual Meeting Swiss League Against Epilepsy (SEL) & Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC) in Basel, Switzerland.

Poster presentation.

Maric A., Werth E., Lustenberger C., Tarnutzer A., Leemann J., Weissengruber S., Ruff C.C., Poryazova R., Huber R., Baumann C.R. (2016).

Comparing the effects of acute and chronic sleep loss on sleep homeostasis, vigilance and decision-making.

Gordon Research Conference (GRC) on Sleep Regulation & Function in Galveston, TX, USA.

Poster presentation.

Maric A., Lustenberger C., Werth E., Leemann J., Huber R.*, Baumann C.R.*, Poryazova R.* (2015). *shared last authorship

Slow wave activity increase after acute sleep deprivation and after chronic sleep restriction.

45th Annual Meeting of the Society for Neuroscience (SfN) – Neuroscience in Chicago, IL, USA.

Poster presentation.

Maric A., Lustenberger C., Werth E., Leemann J., Huber R.*, Baumann C.R.*, Poryazova R.* (2015). *shared last authorship

Impact of acute sleep deprivation and chronic sleep restriction on slow wave activity and vigilance.

Joint Annual Meeting Swiss Society of Pediatrics (SSP) & Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC) in Interlaken, Switzerland.

Poster presentation.

Maric A., Lustenberger C., Werth E., Leemann J., Huber R.*, Baumann C.R.*, Poryazova R.* (2015). *shared last authorship

Slow Wave Activity and Vigilance Changes after Acute Sleep Deprivation and Chronic Sleep Restriction. *29th Annual Meeting of the Associated Professional Sleep Societies (APSS) - Sleep in Seattle, WA, USA*.

Poster presentation.

Maric A., Lustenberger C., Leemann J., Werth E., Tarnutzer A., Pangalu A., Huber R.*, Baumann C.R.*, Poryazova R.* (2015). *shared last authorship

Vigilance and Cortical Excitability after Acute Sleep Deprivation and Chronic Sleep Restriction. *29th Annual Meeting of the Associated Professional Sleep Societies (APSS) - Sleep in Seattle, WA, USA*.

Oral presentation.

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Slow Wave Activity and Vigilance Changes after Acute Sleep Deprivation and Chronic Sleep Restriction.

Clinical Research Day 2015 at the University Hospital in Zurich, Switzerland.

Poster presentation.

Maric A., Lustenberger C., Leemann J., Werth E., Tarnutzer A., Pangalu A., Huber R.*, Baumann C.R.*, Poryazova R.* (2015). *shared last authorship

Vigilance and cortical excitability after acute sleep deprivation and chronic sleep restriction.

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Vigilance and cortical excitability after acute sleep deprivation and chronic sleep restriction.

Symposium of the Clinical Research Priority Program «Sleep and Health» 2015 in Zurich, Switzerland.

Poster presentation.

Maric A., Lustenberger C., Leemann J., Werth E., Gilgen F., Wettstein C., Tarnutzer A., Pangalu A., Huber R.*, Baumann C.R.*, Poryazova R.* (2014). *shared last authorship

Vigilance and cortical excitability after acute sleep deprivation and chronic sleep restriction.

22nd Congress of the European Sleep Research Society (ESRS) in Tallinn, Estonia.

Poster presentation.

Maric A., Lustenberger C., Leemann J., Werth E., Tarnutzer A., Pangalu A., Huber R.*, Baumann C.R.*, Poryazova R.* (2014). *shared last authorship

Vigilance and cortical excitability after acute sleep deprivation and chronic sleep restriction.

Joint Annual Meeting Swiss Headache Society (SHS) & Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC) in Lucerne, Switzerland.

Poster presentation.

Maric A., Lustenberger C., Dürr R., Achermann P., Huber R. (2012).
The associations between sleep spindle activity, general cognitive ability and declarative learning.
21st Congress of the European Sleep Research Society (ESRS) in Paris, France.
Poster presentation.

Maric A. (2012).
Trait-like Sleep Spindle Activity, General Cognitive Ability and Their Association to Overnight Performance Improvement and Learning Efficiency.
Master thesis under supervision of Prof. Dr. Lutz Jäncke, Division of Neuropsychology, Institute of Psychology, University of Zurich, Switzerland and Prof. Dr. Reto Huber, University Children's Hospital Zurich, Switzerland.

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Trait-like sleep spindle activity, information processing speed and their association to sleep-dependent performance improvement.
7th symposium of the Zurich Center for Integrative Human Physiology (ZIHP) in Zurich, Switzerland.
Poster presentation.

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